The Journal of Pediatrics

VOL. 40 FEBRUARY, 1952 NO. 2

SUBACUTE MERCURY POISONING (ACRODYNIA) CAUSED BY PROTIODIDE OF MERCURY

SUCCESSFUL TREATMENT WITH BAL

ALFRED E. FISCHER, M.D., AND HORACE L. HODES, M.D.
NEW YORK, N. Y.

WARKANY and Hubbard in 1948[1] were the first to report the presence of mercury in the urine of children with acrodynia. This important finding suggested to Bivings and Lewis the use of BAL* for removing the mercury from the body.[2] Bivings[3] subsequently collected a number of cases, including those of Elmore,[4] in which clinical improvement followed the use of BAL. Other reports of the successful use of BAL in the treatment of acrodynia were made subsequently by Carithers,[5] and by Warkany and Hubbard,[6] who have recently published a review of the entire subject.[7]

Most of the patients with acrodynia whose clinical histories have been described in the literature had become ill following "teething powders"[8] or "worm cures,"[9] both of which contain calomel (mercurous chloride). The following case report is the first in which protiodide of mercury, prescribed for the treatment of warts, was the offending agent. The recent review by Warkany and Hubbard[7] does not contain a similar case. Although a tentative diagnosis of acrodynia in our case was made because of a history of ingestion of the mercurial salt, mercury was not isolated in the first sample of urine tested. It was found subsequently only after BAL was administered. Therefore, our case is being reported also because it suggests the possibility that BAL may be of use as a diagnostic as well as a therapeutic agent.

CASE REPORT

M. L., a 3½-year-old male, an only child, was first seen on Jan. 17, 1950. The child ate poorly and vomited a great deal during infancy, and had a low vitamin intake. His speech was retarded and at 3½ years he spoke only jargon. In October, 1949, the mother took him to a dermatologist for treatment of several warts about his eyes and mouth. Protiodide of mercury ⅛ gr. (7.5 mg.) t.i.d. was prescribed. The drug was taken for twelve days during early November. During this period the patient had three to four loose stools daily. After thirty-six pills had been consumed, the mother reordered them without consulting her physician, and administered the mercury salt for an additional twelve-day period (until December 7). At the end of that time, because no change in the warts occurred, a second visit was made to the dermatologist who again prescribed pro-

From the Department of Pediatrics, Mount Sinai Hospital.

*Ten per cent solution of dimercaprol in peanut oil with 20 per cent benzyl benzoate. Hynson, Westcott and Dunning, Inc., Baltimore, Md. The name BAL will be used in this report.

tiodide of mercury since he was unaware that a second course of the drug had been given. Shortly thereafter the child's stools again became watery. About December 20 the child became irritable and complained of pain in the legs and knees. Early in January he developed a mild upper respiratory infection with fever, and his eyes "looked heavy." At that time a blood count, sedimentation rate, and urinalysis were found to be normal. The child continued to complain and cried out in his sleep. He developed a reversal of sleep habits, frequently being awake for hours at night and sleeping restlessly during the day. He often assumed a squatting position which apparently gave him some relief from the pain in the legs. The child became more irritable, repeatedly shielded his eyes, and complained that he could not see. As his illness progressed he kept his eyes shut almost continuously. A few days before entry into the hospital, an ophthalmologist found no abnormality in the lids, cornea, or lens.

The patient was seen for the first time by one of us (A.E.F.) on Jan. 17, 1950. He walked with head lowered and eyes tightly shut crying "Can't see, can't see." He whined and cried continually. He was thin and undernourished, and weighed only 25 pounds 13 ounces (11.7 kilograms) as compared with a reported weight of 27 pounds 8 ounces (12.5 kilograms) ten days previously. Pulse was rapid, blood pressure was 100/60. Bright light directed into his eyes produced great discomfort. The neurological examination was entirely negative. Because of the history of ingestion of mercury and the presence of intense and persistent photophobia, a tentative diagnosis of acrodynia due to mercury intoxication was made.

He was admitted to The Mount Sinai Hospital (Case No. 606495) on January 19. Laboratory findings on that day were as follows: hemoglobin 12.4 grams, red blood count 5,070,000, white blood count 13,400, 79 per cent polymorphonuclear cells and 21 per cent lymphocytes. There was no basophilic stippling of the red cells. Urine was negative for albumin and sugar. The spinal fluid examination revealed no increase in cells, a normal concentration of sugar, and a total protein content of 56 mg. per cent. X-ray examination of the long bones showed no zones of increased density. Roentgenograms of the skull showed a normal outline of the sella turcica and gave no evidence of increased intracranial pressure. There was no abnormality in the bones of the calvarium. An electroencephalogram revealed no significant changes.

Examination on admission to the hospital revealed findings similar to those noted above. Photophobia was very marked causing the child to lie frequently in a jackknife position with his head buried in the pillow. He was quite hypotonic. A psychological evaluation showed that intellectually he was functioning within the normal range. It was not possible to determine whether the overt behavior which he exhibited was on an organic or functional basis, but his grasp of language was normal and comprehension and memory processes were adequate.

The child was observed and studied at the hospital for a week without therapy in an attempt to rule out an organic neurological condition or early schizophrenia. His appetite continued to be poor, he perspired profusely, lost weight, remained irritable and failed to show any interest in his surroundings. Urine collected on January 26 gave a negative reaction when tested for the presence of a heavy metal by the Ganassini modification of the Reinsch test (for details of the method see Reiner[10]). This test is positive when a concentration of mercury greater than 25 gamma per liter is present and is negative below this level.[11]

Since the patient exhibited so many of the symptoms of acrodynia it was decided on January 31 to start treatment with BAL, despite the fact that the urine was reported to contain no mercury on the first examination. He was given 20 mg. of BAL (1.7 mg. per kilo) every four hours by intramuscular injection on the first day and 30 mg. every four hours on the second day. He received 40 mg. of BAL every four hours (omitting one dose at night) for the next four days, and 40 mg. every eight hours for the next ten days. The total quantity administered was 2,300 mg. given over a period of sixteen days. Novocain was not used since there was little pain following the injections. Slight local irritation in each buttock was observed but disappeared a few days after cessation of therapy. The dosage of BAL which was employed for our patient was similar to that used in the treatment of lead poisoning.[12] A number of systemic toxic effects of BAL have been described, including nausea, vomiting, lacrimation, paresthesias, and abdominal pain[13]; despite the prolonged course of therapy, none of these was observed in our patient.

Beginning January 30, an attempt was made to examine all urine for mercury, but some loss was encountered on several occasions because of the child's lack of cooperation. All specimens were collected in a container that had been carefully washed to remove any trace of bichloride of mercury solution which might have been used for disinfection. As shown in Table I, the urine obtained on Jan. 26, 1950, six days before BAL was administered, was reported negative for mercury. The second three-day specimen, which was collected one day before the injection of BAL as well as during the first two days of BAL therapy, contained 333 gamma of mercury per liter, while the next three-day specimen, collected during the third, fourth, and fifth days of treatment with BAL, showed a concentration of mercury of 500 gamma per liter. Thereafter, despite continued use of BAL, the concentration of mercury in the urine declined rapidly and was found to be within normal limits during the ninth, tenth, and eleventh days.

TABLE I

SPECIMEN NO.	DATE	QUANTITY OF URINE (C.C.)	TOTAL AMOUNT OF MERCURY IN URINE SPECIMEN (MG.)	CONCENTRATION OF MERCURY IN URINE (GAMMA PER LITER)
1	1-26-50	300	None†	None†
2	1-30, 1-31,* 2-1	900	0.3	333
3	2-3, 2-4, 2-5	500	0.25	500
4	2-6, 2-7, 2-8	600	0.03	50
5	2-9, 2-10, 2-11	650	0.01	15

*BAL begun this date.

†This estimation was made according to the modified Reinsch method which detects concentrations of mercury greater than 25 gamma per liter only. All subsequent determinations were carried out according to the method of Gettler and Lehman[14] by Mr. Harry Schwartz, Toxicologist, Medical Examiner's Office, City of New York.

No striking change occurred in the child's condition until a week after BAL therapy was begun. At that time his appetite began to improve, he became much less irritable, and was more active about the ward. On about the tenth day of treatment photophobia was less marked. The patient now looked up from the floor for short

periods of time. His improvement continued despite an intercurrent respiratory infection. By February 15, the sixteenth and final day of treatment, his eyes were kept open for several minutes at a time and he showed little photophobia except when bright light was flashed directly into his eyes. He gained weight and on the day of discharge from the hospital reached 27 pounds 3 ounces (12.4 kilograms), which was 1 pound 6 ounces (0.72 kilogram) above his weight on admission. His improvement continued at home. He fed himself, was quite cooperative, and slept well at night. On March 1, it was noted that he was losing hair, and the alopecia became quite marked after a severe upper respiratory infection later that month. On March 15, no photophobia was noted on exposure to ordinary light, although some discomfort was elicited on looking into a floodlight. When examined on April 19, 1950, the child appeared entirely well.

In summary, our patient had the following symptoms: irritability, painful lower extremities, hypotonia, photophobia, alopecia, slight fever, excessive perspiration, diarrhea, salivation, loss of weight, tachycardia, and anorexia. He slept in a crouched position during the day but was wakeful at night, moaning and crying. Certain other symptoms sometimes encountered in patients with acrodynia were not present; these include erythema and coldness of the hands and feet, lacrimation, and hypertension. Albuminuria and glycosuria, findings described by Ross,[15] were also absent.

ETIOLOGY

The cause of acrodynia was entirely unknown[16] until the Kettering Laboratory in Cincinnati, making an examination for heavy metals at the request of Warkany,[1] found mercury in the urine of a child with acrodynia. Bivings[3] reported that Lesesne Smith, Sr., W. C. Davison, and John Zahorsky among others had suspected that mercury was involved in the cause of acrodynia. Arsenic had been isolated in a few instances by early workers.[17, 18, 19] Fanconi and associates in 1947 reported that children in Switzerland who were taking "worm cures" sometimes developed the acrodynia syndrome or Feer's disease, as it is known there,[9] but prior to Warkany and Hubbard's publication in 1948 no one had definitely linked the absorption and excretion of mercury to acrodynia.[1] Predisposition, hypersensitivity and a "neuro-allergic" reaction influencing the vegetative nervous system were brought forward as possible explanations for the relative rarity of acrodynia when compared with the number of children who ingest mercury, especially in the Southern sections of the United States, the British Isles, Australia, and Switzerland.

It was stated[9] that some of the children who showed symptoms of acrodynia following mercury ingestion might have been ill even before the administration of calomel was begun. This possibility was also considered by Hansen[20] and Warkany.[6] Our patient might have been considered a candidate for "teething powders" for he was extremely tense and certainly was a "high-strung" child. However, it is quite clear that he was well except for "nervousness" until three or four weeks after he started to take the mercury. Vitamin deficiency was formerly considered to be a likely etiological factor in acrodynia, and diseases of

the teeth and gums were said to be a frequent feature of the disease as described by early authors.[16, 21] Recent case reports do not record the presence of gingivitis or diseased teeth. It may very well have been that patients formerly described did have some vitamin deficiencies, as most of them came from families in poor economic circumstances and were probably fed incomplete diets.

Since arsenic has been definitely incriminated only a few times, mercury must be considered the cause of acrodynia in nearly every instance (92.7 per cent of Warkany and Hubbard's cases[7]).

TYPES OF REACTION TO MERCURY

The absorption of mercury by the infant or young child may be followed by a variety of symptom complexes. There is need to define these and to consider the relation of acrodynia to other syndromes caused by mercury.

Acute poisoning results from the ingestion of a soluble salt of mercury, such as the bichloride, or from absorption of an ointment containing a high content of metallic mercury or mercuric oxide.[3, 8, 22a, b, d] If a sufficient quantity of the metal reaches the kidney, tubular damage results. Anuria followed by edema, convulsions, uremia, and death may result. The severity of the injury depends in general upon the quantity of mercury ingested. It is stated that in adults 1.5 Gm. of mercury bichloride taken by mouth often result in death, that the prognosis is poor when 1.0 Gm. is taken, and that 0.5 Gm. is rarely if ever fatal.

Smaller quantities of the metal absorbed for short periods of time often prove harmless, but in some instances they cause irritability, diarrhea, polyuria, low-grade fever, or a morbilliform rash.[8, 16b] There are also individuals who exhibit an idiosynerasy to mercury and may react severely to a very small quantity of the metal or its salts. Violent febrile reactions associated with marked skin erythema and edema of subcutaneous tissue are the usual symptoms of this type of sensitivity. Instances of such unusual susceptibility have been described by Bass and have occurred following the handling of glassware containing mercury, as the result of mercury amalgam filling in teeth[22c] and after the use of diapers which have been rinsed in bichloride of mercury solution.[3] Patients showing this type of reaction usually recover promptly when the causative agent is removed.

When small quantities of mercury are taken in the form of tablets, powders, and ointments for periods of days or weeks, some individuals develop symptoms and signs which are similar to and identical with those described in acrodynia. As noted by Carithers,[5] the complete picture of acrodynia as described by Bilderback[16] need not be present. In Carithers' patient, pronounced photophobia, slight hypertension, anorexia, weight loss, irritability, muscle weakness, and a skin rash were present. Signs of acute mercury poisoning, such as high fever, erysipeloid lesions, generalized edema, prostration, and unconsciousness are absent in patients with acrodynia. It is worth noting that ingestion of mercury does not produce roentgenographic changes in the long bones as do lead and bismuth. It is further to be noted that stippling of red cells, which is common in patients

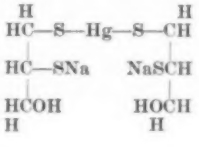
with lead poisoning, does not occur in patients with acrodynia.

Since most persons are not affected by therapeutic doses of mercury, the theory of increased susceptibility in explaining some cases of mercury intoxication seems plausible.[5] In fact, some individuals may excrete detectable amounts of the metal in the urine without exhibiting clinical signs of illness. Three of the patients described by Warkany and Hubbard[6] who were known to have swallowed mercury remained entirely well, though 50, 70, and 180 gamma per liter, respectively, were found in their urine. Also mercury has been found occasionally in the urine of normal individuals, but rarely in a concentration above 50 gamma per liter.[6]

In reviewing the literature, therefore, one is impressed by the varying degrees of reaction to the metal, the difference in the time interval between the first dose of mercury and the onset of clinical symptoms in various patients, and also by the differences in the quantities of mercury ingested. Some children, like those reported by Elmore,[4] had taken only "a few teething powders," each of which contained 3.5 mg. of mercurous chloride. Bivings and Lewis'[2] patient also became ill after only a small amount of mercury. On the other hand, our patient, who was 3½ years old, swallowed approximately 22.5 mg. a day for two twelve-day periods, and then after several weeks again took approximately 15 mg. a day for perhaps another week before he became ill. Since the protiodide of mercury is a soluble compound, the amount absorbed must have been large, though the absorption may have been limited somewhat by the diarrhea.

TREATMENT WITH BAL

The demonstration of the probable etiological role of mercury in acrodynia led Bivings and Lewis[2] in 1948 to employ BAL, apparently with success, in the treatment of an infant suffering from this disease. The use of BAL (dimercaptopropanol) in combating the effects of acute mercury poisoning is based upon sound experimental and clinical evidence[23] which can be described here only very briefly. It has been shown that heavy metals such as arsenic and mercury are toxic to biological systems because they combine with SH groups of the protein moiety of cellular enzymes to form mercaptides. Peters, Stocken, and Thompson[24] found that simple 1,2 dithiols such as BAL (CH_2SH . CHSH . CH_2OH) are capable of preventing such combination and are able to reverse them after they have become established. The effectiveness of BAL in arsenic poisoning is believed to be due to its reaction with the metal to form a stable ring compound. In this way it competes effectively for the arsenicals with the thiol groups of tissue proteins. The removal of the arsenic from the tissue protein is followed by its rapid excretion in the urine.[25a, b, c] In the case of mercury, a similar mechanism is postulated with the formation of a mercury-BAL compound. This compound is soluble but only very slightly dissociated, and it probably also is excreted rapidly in the urine. It is formed in a slightly alkaline medium such as prevails in vivo. Gilman and his associates[25d] believe that it is of the following nature:



There is little doubt that BAL is effective in acute mercury poisoning in animals and man,[25e] but it cannot be assumed that it therefore will be of great value in the more chronic type of mercury poisoning which causes acrodynia. Evidence is accumulating, however, which indicates that BAL is at least of some value in relieving the symptoms of acrodynia. As we have stated, Bivings and Lewis[2] in 1948 reported the successful use of BAL in acrodynia. A year later Bivings[3] collected from the literature reports of eleven instances in which rapid improvement followed the use of BAL and four cases in which the beneficial effect of the drug was apparent only after a rather long interval. Among others, Bivings,[3] Elmore,[4] Carithers,[5] Boyd,[26] and Fanconi and Botsztejn[27] reported their experiences with BAL. Some of the reports are cautious, and apparently not all patients responded rapidly. However, one hardly would expect all symptoms of acrodynia to disappear promptly. The union of mercury with the cell and the damage caused thereby cannot be repaired quickly if the pathological process has been of long duration.

Improvement in our patient began after the first week of therapy and was quite striking after the second week. Treatment was continued for sixteen days because there were no toxic effects caused by BAL, and because mercury was still present in the urine in low concentration after twelve days of therapy. Although our patient had been ill for ten weeks, he was worse when treatment was begun than at any time during his illness. It seemed clear to all of those who observed this patient that the beginning of his improvement coincided with the administration of BAL. At the same time, increased amounts of mercury were being excreted. Indeed, had BAL not been given, mercury might not have been found in detectable amounts. Our experience in this case suggests that BAL is of value as a diagnostic measure in those cases in which acrodynia is suspected but in which the urine examination for mercury yields negative or doubtful results.[28]

Van Creveld and Paulssen[29] recently called attention to the increased excretion of mercury during BAL therapy. Their figures are not as striking as those recorded in our patient. Case 34 in Warkany and Hubbard's report[7] also showed a similar effect. However, in their Case 35, as well as in Carithers'[5] patient, a large amount of mercury was being eliminated before the administration of BAL, and no further increase was demonstrated. Boyd[26] described a patient of Gibson,[30] who recovered promptly following treatment with BAL despite the fact that no mercury was found in the urine before, during, and after completion of therapy. A possible explanation for the failure to detect mercury in this case may be found in the fact that the urine specimens were examined by Biancolini's method, which is a qualitative test said to give a positive reaction only when a concentration of mercury of 50 gamma per liter or more is present.[31]

Our case illustrates the need for repeated examination of the urine until both clinical improvement has occurred and the presence of mercury has been confirmed. A sensitive test, such as that of Warkany and Hubbard, or Gettler and Lehman, must be employed. BAL apparently begins to exert its influence very promptly so that, if no mercury is found after

three days of therapy, one may be reasonably certain that mercury has not been retained in the body.

CONCLUSIONS

1. The case history of a child suffering from subacute mercury poisoning following the ingestion of protiodide of mercury is described.

2. Treatment with BAL was successful. Improvement was noted about eight days after institution of therapy and complete recovery followed.

3. The diagnostic importance of an increase in the excretion of mercury in a suspected case of acrodynia following the administration of BAL is discussed.

REFERENCES

1. Warkany, J., and Hubbard, D. M.: Mercury in the Urine in Acrodynia, Lancet **1:** 829, 1948.
2. Bivings, L., and Lewis, G.: Acrodynia: A New Treatment With BAL, J. PEDIAT. **32:** 63, 1948.
3. Bivings, L.: Acrodynia: A Summary of BAL Therapy Reports and a Case Report of Calomel Disease, J. PEDIAT. **34:** 322, 1949.
4. Elmore, S. E.: Ingestion of Mercury as a Probable Cause of Acrodynia and Its Treatment With Dimercaprol (BAL): Report of Two Cases, Pediatrics **1:** 643, 1948.
5. Carithers, H. A.: Mercury Poisoning Producing Acrodynia: Treatment With Dimercaprol, Pediatrics **4:** 820, 1949.
6. Warkany, J., and Hubbard, D. M.: Mercury in the Urine of Children With Acrodynia, Tr. American Pediatric Society, Atlantic City, N. J., May 5, 1949, Abstr. Am. J. Dis. Child. **79:** 388, 1950.
7. Warkany, J., and Hubbard, D. M.: Adverse Mercurial Reactions in the Form of Acrodynia and Related Conditions, Am. J. Dis. Child **81:** 335, 1951.
8. Annotation, Pink Disease, Lancet **1:** 644, 1948.
9. Fanconi, G., Botsztejn, A., and Schenker, P.: Ueberempfindlichkeitsreacktionen auf Quecksilbermedikation im Kindesalter mit besonderer Berücksichtigung der Calomelkrankheit, Helvet. pediat. acta Beilage **2:** (Supp. 4), 1947.
10. Reiner, M.: Manual of Clinical Chemistry, New York, 1941, Interscience Publishers, Inc., p. 195.
11. Gettler, A. O.: Personal communication to authors.
12. Ennis, J. M., and Harrison, H. E.: Treatment of Lead Encephalopathy with BAL (2,3 Dimercaptopropanol), Pediatrics **5:** 853, 1950.
13. Sulzberger, M. B., Baer, R. L., and Kanof, A. J.: Clinical Uses of 2,3 Dimercaptopropanol (BAL). III. Studies on Toxicity of BAL on Percutaneous and Parenteral Administration, J. Clin. Investigation **25:** 474, 1946.
14. Gettler, A. O., and Lehman, R.: A Simplified Procedure for the Determination of Mercury in Urine, Am. J. Clin. Path., Tech. Supp. **8:** 161, 1938.
15. Ross, S. G.: Discussion of Warkany and Hubbard,[6] Am. J. Dis. Child. **79:** 392, 1950.
16. (a) Bilderback, J. B.: Acrodynia. Brennemann's Practice of Pediatrics, Hagerstown, Md., 1948, W. F. Prior Co., Inc., vol. 4, chap. 20.
    (b) Bilderback, J. B.: Discussion of Warkany and Hubbard,[6] Am. J. Dis. Child. **79:** 391, 1950.
17. Meyer, F., and Weise, E. C.: Acrodynia: Arsenic as the Etiologic Factor, J. PEDIAT. **2:** 750, 1933.
18. Calvin, C. V., and Taylor, C. C.: Acrodynia: Its Possible Cause, J. PEDIAT. **6:** 385, 1935.
19. Ecker, A. D.: Arsenical Content of the Brain in Cases of Encephalitis, Inflammatory Occlusion of Aqueduct, and Acrodynia, Proc. Staff Meet., Mayo Clin. **14:** 43, 1939.
20. Hansen, A. E.: Discussion of Warkany and Hubbard,[6] Am. J. Dis. Child. **79:** 392, 1950.
21. (a) Weston, W.: Acrodynia, Arch. Pediat. **37:** 513, 1920.
    (b) Brown, A., Courtney, A. M., and MacLachlan, I. F.: Clinical and Metabolic Study of Acrodynia, Arch. Pediat. **38:** 609, 1921.
    (c) Tisdall, F. F., Drake, T. G. H., and Brown, A.: Nicotinic Acid in Treatment of Acrodynia, J. PEDIAT. **13:** 891, 1938.
    (d) Durand, J. I., Spickard, V. W., and Burgess, E.: Acrodynia Treated With Intramuscular Injections of Vitamin B_1, J. PEDIAT. **14:** 72, 1939.
    (e) McNeal, M. D.: Five Cases of So-Called Acrodynia, Minnesota Med. **5:** 153, 1939.
    (f) Cobb, C.: Acrodynia, Am. J. Dis. Child **46:** 1076, 1933.
22. (a) Harper, P.: Idiosyncracy to Ammoniated Mercury Ointment: Report of Two Cases, J. PEDIAT. **5:** 794, 1934.
    (b) Bass, M. H.: Idiosyncrasy to Ammoniated Mercury, J. Mt. Sinai Hosp. **10:** 199, 1943.
    (c) Bass, M. H.: Idiosyncrasy to Metallic Mercury With Special Reference to Amalgam Fillings in the Teeth, J. PEDIAT. **23:** 215, 1943.

(d) Bass, M. H.: Idiosyncrasy to Ammoniated Mercury Ointment in Childhood, Urol. Cut. Rev. **45**: 78, 1941.

23. Longcope, W. T., and Luetscher, J. A.: Treatment of Acute Mercury Poisoning by BAL, J. Clin. Investigation **25**: 557, 1946.
24. Peters, R. A., Stocken, L. A., and Thompson, R. H. S.: Nature **156**: 616, 1945.
25. (a) Carleton, A. B., Peters, R. A., Stocken, L. A., Thompson, R. H. S., Williams, D. E., Storey, T. B. E., Levy, G. A., and Chance, A. C.: The Treatment of Complications of Arseno-Therapy With BAL, J. Clin. Investigation **25**: 497, 1946.
(b) Barron, E. S. G., and Singer, T. P.: Enzyme Systems Containing Active Sulfhydryl Groups. The Role of Glutathione, Science **97**: 356, 1943.
(c) Eagle, H., Magnuson, H. J., and Fleischman, R.: Systemic Treatment of Arsenic Poisoning With BAL, J. Clin. Investigation **25**: 451, 1946.
(d) Gilman, A., Allen, R. P., Philips, F. S., and St. John, E. J.: The Treatment of Acute Systemic Mercury Poisoning in Experimental Animals With BAL, Thiosorbitol and BAL Glucoside, J. Clin. Investigation **25**: 549, 1946.
(e) Williams, B. H., and Beach, W. C.: Idiosyncrasy to Ammoniated Mercury. Treatment with 2,3 Dimercaptopropanol (BAL), J. A. M. A. **142**: 1286, 1950.
26. Boyd, J. D.: Discussion of Warkany and Hubbard,[6] Am. J. Dis. Child. **79**: 391, 1950.
27. Fanconi, G., and Botsztejn, A.: Die Feersche Krankheit (Akrodynie) und Quecksilbermedikation, Helvet. paediat. acta **3**: 264, 1948.
28. Fischer, A. E.: Discussion of Bivings, Lee. Résumés des Communications. Sixth International Congress for Pediatrics, July, 1950, Zurich, Switzerland, p. 401.
29. Van Creveld, S., and Paulssen, M. M. P.: Acrodynia and Mercury Poisoning, Acta paediat. **38**: 82, 1949.
30. Gibson, P. E.: Personal communication.
31. Pheteplace, W. S.: Personal communication.

INVESTIGATIONS ON THE BACTERIAL FLORA, pH, AND SUGAR CONTENT IN THE INTESTINAL TRACT OF INFANTS

GIULIO J. BARBERO, M.D., GRETCHEN RUNGE, M.D., DOANE FISCHER, M.D., MARY N. CRAWFORD, M.D., FRANCISCO E. TORRES, M.D., AND PAUL GYÖRGY, M.D.
PHILADELPHIA, PA.

INTRODUCTION

IT HAS been known since the original studies of Tissier and Moro that the stool of the infant fed human milk is more acid and contains a much higher percentage of gram-positive bacilli, in particular *Lactobacillus bifidus*, than the stool of the infant fed cow's milk.[1, 2, 3] The development and maintenance of this bifidus flora in the stool of breast-fed infants has generally been thought to be related to the low protein and high lactose content of human milk.[4, 5] From a more teleological point of view, lactose as the specific sugar of milk may be necessary for the promotion of a predominantly bifidus flora, found only in the normal breast-fed infant.

In the voluminous literature on bifidus flora there are few investigations on record concerning the localization of this flora in the intestinal tract of breast-fed infants. Apparently no studies have been reported concerning the bacterial flora and pH of the contents of various intestinal segments in the living infant. This paper presents findings on the bacterial flora and the pH of the intestinal contents of infants fed solely a diet of either human or cow's milk.

In addition, in a large number of infants fed breast milk or various milk mixtures bacterioscopic examinations and pH determinations on the stools were carried out in order to confirm results reported in the earlier investigations and for comparison with data obtained by intestinal intubation. Formulas of evaporated milk (with maltose-dextrin mixtures as carbohydrate supplement) and various brands of commercially available infant formulas whose proximate analysis is comparable to human milk were used (SMA, Similac, Bremil). Further, special modifications of one of the infant formulas (SMA) were also studied. These modifications were based mainly on the results obtained in the course of the study[6] of the in vitro cultural and growth requirement of *L. bifidus* and its mutant (*L. acidophilus*). These investigations demonstrated that short chain saturated fatty acids C_8-C_{14} strongly inhibit the growth of both *L. bifidus* and *L. acidophilus*.[7, 8] Of the short chain saturated fatty acids, the C_8 and C_{10} members of the series inhibited growth of *Escherichia coli* and *Aerobacter aerogenes* as well, although the inhibition was less than for Lactobacilli.[8]

METHODS

The stools were obtained from normal infants between the ages of 2 weeks and 3 months. Approximately one-half gram of stool was taken from the rectum with a sterile swab, and

From the Department of Pediatrics, School of Medicine, University of Pennsylvania.

This study was supported by a research grant from Wyeth, Incorporated, Philadelphia.

suspended in 10 ml. of sterile, distilled water. On part of this diluted specimen, the pH was determined with the Beckman glass electrode. A thin smear was made, fixed with heat, and stained with Gram's stain. One hundred bacterial cells were counted and differentiated by staining reaction and morphology. Plate cultures were made (Brewer jars) of some of the stool suspensions. The plates were incubated at 37° C. under anaerobic conditions with 10 per cent carbon dioxide. A modification of the Teply and Elvehjem medium[9] was used.[6]

Seven infants fed human milk and eight infants fed formula with evaporated milk were used for intubation studies. The infants were maintained on the same feeding schedule during the intubation period. A No. 12 Infant Miller-Abbott tube with the balloon over the terminal portion was inserted through the mouth into the stomach and allowed to pass into the duodenum, stimulated by gentle massage of the abdomen under fluoroscopic guidance. Passage into the duodenum was usually rapid and was recognized by (1) a characteristic loop sharply angulated to the left seen by fluoroscopy as pictured in Fig. 1, (2) the resistance to the injection of 5 ml. of air into the balloon, and (3) a yellow-tinged drainage fluid with an alkaline shift in the pH. Once the tube was in

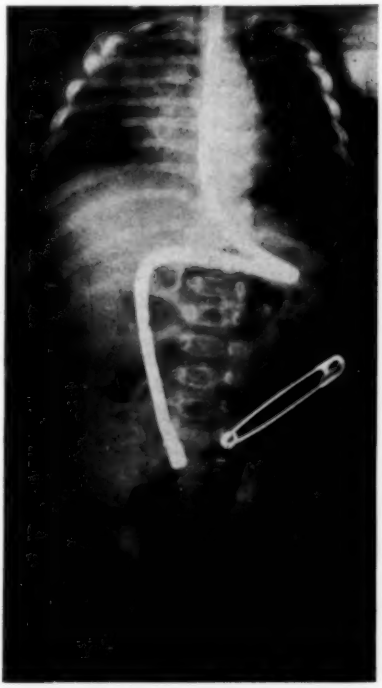


Fig. 1.

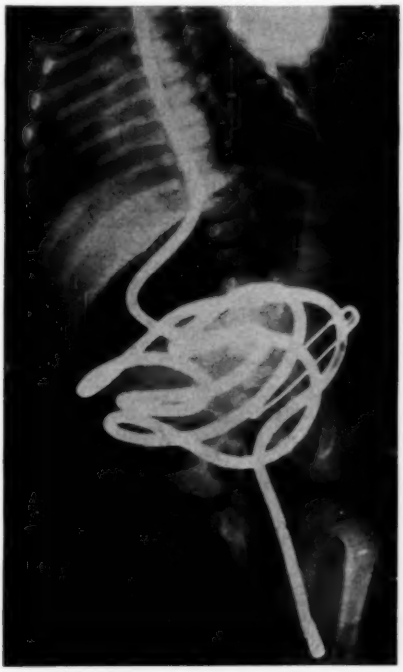


Fig. 2.

Fig. 1.—Miller-Abbott tube in the duodenum.
Fig. 2.—Miller-Abbott tube through entire intestine.

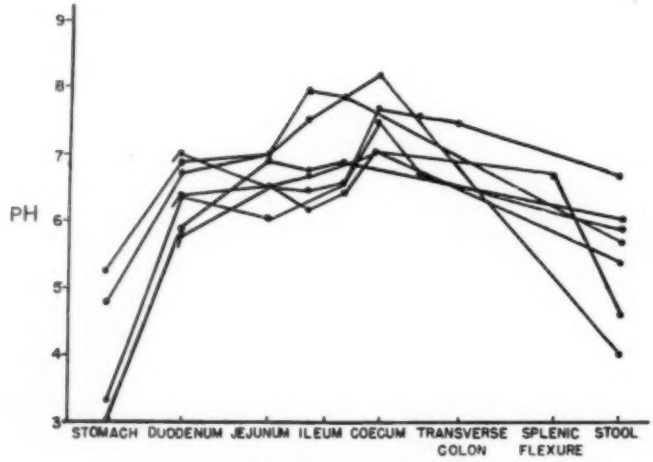


Fig. 3.—pH of intestinal contents of breast-fed infants.

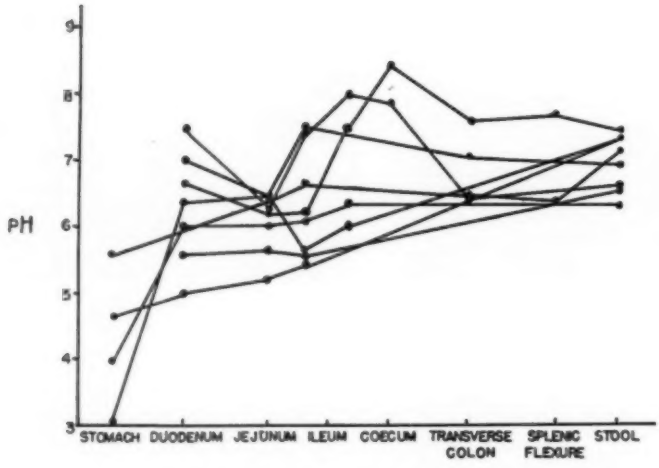


Fig. 4.—pH of intestinal contents of infants fed cow's milk.

the duodenum, the balloon was inflated with 5 to 8 ml. of air and continuous suction applied. At successive levels in the course of the passage of the tube down to the rectum, samples of enteric fluid were obtained for study. The tube passed rapidly to the lower ileum, then slowly in the cecum and up into the colon in twenty-four to thirty-six hours. The tube was removed by deflating the balloon and by putting very slight constant tension on it. The entire intestine was frequently telescoped on several loops of the Miller-Abbott tube which, in such cases, would require only 2½ to 3 feet of tubing for its passage from mouth to rectum. Fig. 2 is a typical roentgenogram of a tube which had passed to the rectum. On each drainage specimen, the pH, the differential bacterial count, and the total bacterial count were determined. Some specimens were cultured for the determination of the presence of *L. bifidus* and the total sugar content was determined at the different levels of the intestine of five of the infants. The bacterial count was performed in a Petroff-Hausser bacterial counting chamber. Sugar determinations were carried out by the Folin-Wu method with a filtrate obtained by Somogyi's method.[10]

RESULTS

A. *Studies on Samples Obtained by Intestinal Intubation.*—The enteric fluid obtained by intestinal intubation was a clear yellow-green fluid throughout the duodenum, jejunum, and upper ileum. In the region of the terminal ileum it became rather abruptly a thick, cloudy material composed of yellow curds. From this point on, the drainage fluid became increasingly concentrated. Thick, viscous material was aspirated from the splenic flexure and the descending colon. There was no difference in the color and consistency of the intestinal contents of the infants fed cow's milk and those fed breast milk; however, the enteric contents of the infants fed cow's milk had a definite fecal odor beyond the lower ileum, whereas the samples from the breast-fed infants had no fecal odor.

Figs. 3 and 4 show the pH values of the intestinal contents at various levels. The only difference in the pH of the intestinal contents of the infants fed human and the infants fed evaporated milk formulas was that the pH fell more rapidly in the large intestine of the breast-fed infants. The tendency observed was a rise to a maximum near pH 8.0 in the cecum followed by a fall in pH through the large intestine to the stool. The pH values for the infants fed evaporated milk showed greater variation than those of the infants fed human milk.

The total bacterial counts and the percentage of gram-positive bacilli in the intestinal fluid are summarized in Figs. 5 and 6. Fig. 5 shows that the duodenum contained less than 4,000 bacteria per milliliter. The samples contained increasing numbers of bacteria as the tube passed lower in the intestinal tract. The type of bacterial flora also changed markedly from the small to the large intestine. The flora of the duodenum and jejunum was chiefly cocci, with an occasional bacillus. In the region of the cecum, the flora changed to one with a considerable number of gram-positive bacilli. Fig. 6 shows the percentage counts of the gram-positive bacilli. In four infants fed evaporated milk the relative number of gram-positive bacilli in the

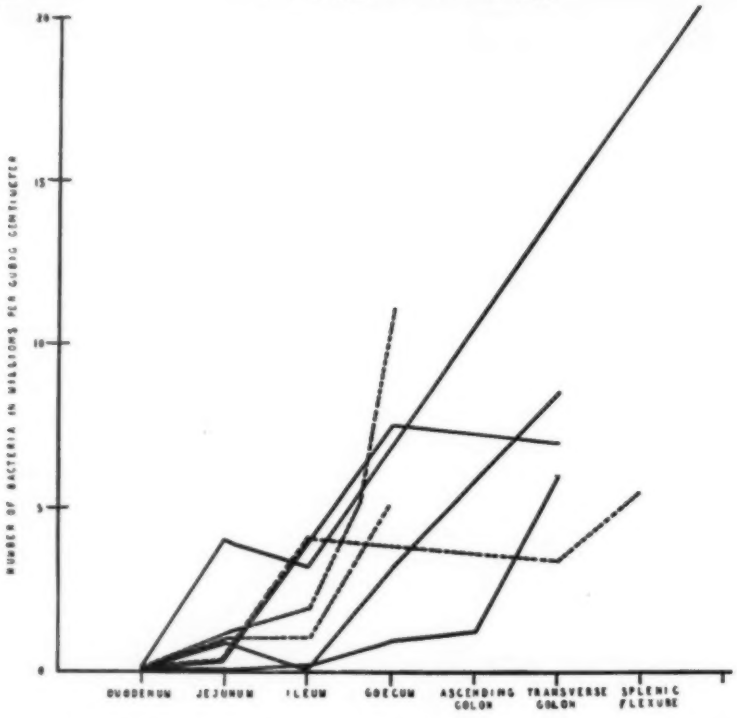


Fig. 5.—Total bacterial counts of intestinal fluid of infants. ——— = Breast-fed infants. - - - - - - - - = Infants fed cow's milk.

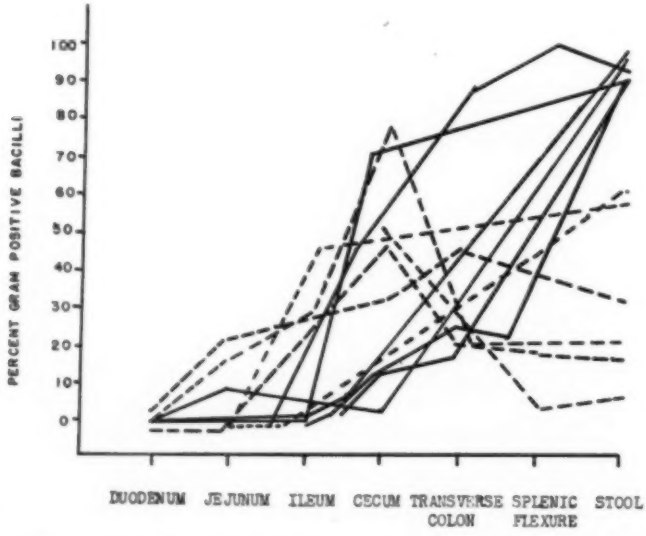


Fig. 6.—Percentage of gram-positive bacilli in the intestinal fluid of infants. ——— = Breast-fed infants. - - - - - - - - = Infants fed cow's milk.

content of the cecum was compared with that found in the stools. In three of these infants the cecal contents showed a higher ratio of gram-positive bacilli to the total count than the stools of the same infants, whereas the corresponding figures on the fourth infant presented no significant difference. In contradistinction to this, the Seven of the infants were fed breast milk and seven were fed cow's milk (Table I). Above the terminal ileum only enterococci were found. In and distal to the ileum, gram-positive bacilli, often with bifid character, were found in both groups of infants. Bacilli with bifid morphology were found in five out of six cultures of stools of

TABLE I. SITES OF CULTURE OF GRAM-POSITIVE BACILLI AT DIFFERENT LEVELS OF THE INTESTINE OF INFANTS

INFANT	DUODENUM	JEJUNUM	ILEUM	CECUM	ASCENDING AND TRANSVERSE COLON	SIGMOID	STOOL
1	NC	NC	*	NC	*Bifid	NC	*Bifid
2	NC	No gram-positive bacilli	NC	*	NC	NC	*
3	NC	NC	No growth	*Bifid	NC	NC	*Bifid
4	NC	NC	*Bifid	NC	NC	NC	NC
5	No growth	No growth	*	*Bifid	*Bifid	NC	*Bifid
6	NC	NC	NC	*Bifid	*Bifid	NC	*Bifid
7	No gram-positive bacilli	No gram-positive bacilli	No growth	*	*	NC	*Bifid
8	No growth	No gram-positive bacilli	No gram-positive bacilli	NC	NC	NC	NC
9	No gram-positive bacilli	No gram-positive bacilli	No growth	No growth	No gram-positive bacilli	NC	NC
10	NC	NC	NC	*Bifid	*Bifid	NC	*
11	NC	NC	NC	NC	*Bifid	NC	*Bifid
12	NC	NC	NC	NC	*Bifid	*Bifid	*Bifid
13	NC	NC	NC	NC	*	*Bifid	*
14	NC	NC	NC	No gram-positive bacilli	*Bifid	NC	*

NC = Not cultured. * = Gram-positive bacilli cultured. *Bifid = Gram-positive bacilli cultured with some bifid forms.

percentage of gram-positive bacilli in the stools of all the breast-fed infants studied was higher than that at any level of the intestinal tract. In the infants fed cow's milk, the gram-negative bacilli became increasingly more prevalent in the lower levels of the intestinal tract.

Samples of intestinal fluids from fourteen infants were cultured.*

breast-fed infants, and in only two out of five stools of infants fed evaporated milk formula.

Sugar determinations were made on the intestinal contents of five infants, three on breast milk and two on cow's milk (Table II). Reducing sugar was found in varying quantity in practically all the samples tested. Infant No. 1 took his feedings very poorly which may account for his over-all low values. Infant No. 5 differed from

*We wish to express our thanks to Thelma Flanders for her assistance in these bacteriological studies.

the others in that a secondary rise in reducing sugar occurred. This rise may be accounted for by concentration of the intestinal fluid in the lower bowel.

B. *Effect of Diet on pH and Percentage of Gram-Positive Bacilli in the Stool.*—The results of the pH determinations of the stools of the infants are shown in Table III. The diets fed were human milk, evaporated milk, and commercial infant formula with a chemical composition approximating that of human milk.

groups are summarized in Figs. 7 and 8. The averages for pH in the six subgroups of infants fed evaporated milk were remarkedly constant whereas the percentage of gram-positive rods in the same groups showed some variations: for pH 6.5, 6.6, 6.6, 6.7, 6.8, 6.9, and for percentage of gram-positive bacilli 44.8, 47.7 50.9, 54.4, 57.6, 61.0.

The stools of breast-fed infants were characterized by a low pH, with an average of 5.5, and by a remarkably uniform, high percentage of gram-positive rods, varying only between 92 to

TABLE II. SUGAR CONTENTS OF INTESTINAL LUMEN AT DIFFERENT LEVELS (MG. %)

	INFANTS FED COW'S MILK		INFANTS FED BREAST MILK		
INTESTINAL LEVEL	1	2	3	4	5
Stomach	--	---	359	---	---
Duodenum	11	15	394	27	839
Jejunum	25	136	797	887	858
Ileum	25	572	167	170	146
Cecum	54	31	18	236	218
Ascending colon	14	---	22	---	416
Transverse colon	1	54	---	---	---

TABLE III. EFFECT OF DIET ON pH AND PERCENTAGE OF GRAM-POSITIVE BACILLI

		pH			GRAM-POSITIVE RODS	
TYPE DIET	NO. OF INFANTS	STOOLS EXAMINED	pH AVERAGE AND RANGE		STOOLS EXAMINED	AV. %
I. Human milk	22	121	5.5	(4.3-7.5)	121	97.4
II. Evaporated milk	130	542	6.7	(4.7-8.8)	362	53.4
III. SMA 1	26	167	6.5	(4.4-8.1)	107	66.8
SMA 3*	18	90	5.7	(4.8-7.1)	79	80.7
SMA 5	11	77	5.6	(4.6-7.9)	77	75.9
IV. Similac	12	77	6.2	(5.0-7.7)	77	56.3
V. Bremil	17	127	6.55	(4.8-8.6)	115	49.4

*Represents SMA currently available.

The data for the group of infants receiving evaporated milk are the average of six subgroups, each of them having been used as simultaneous control for groups of infants fed various types of diet. For instance, the first subgroup comprising 342 pH determinations and 145 bacterioscopic examinations of the stools was compared with the group of breast-fed infants. The corresponding results for these

100 per cent, with an average of 97.4 per cent. The gram-positive bacilli in the stools of the infants fed human milk appeared in the smears as slender rods, uniform in size and staining quality. They were frequently arranged in pairs of parallel groups and showed branching in large numbers. In contrast, bacterioscopic examination of the stools in all other groups showed a more mixed flora, the gram-positive

bacilli varied more in size, shape, and staining quality, and bifid forms were rare.

Cow's milk "adapted" to breast milk should produce more acid pH and a higher average percentage of gram-positive rods in the stools. However, in infants fed SMA 1, Similac, or Bremil, the pH of the stools was only very slightly and insignificantly more acid than that found in infants receiving evaporated milk. The average percentage of gram-positive rods in the stools of infants fed Similac or Bremil showed no difference from that seen in the stools of infants fed evaporated

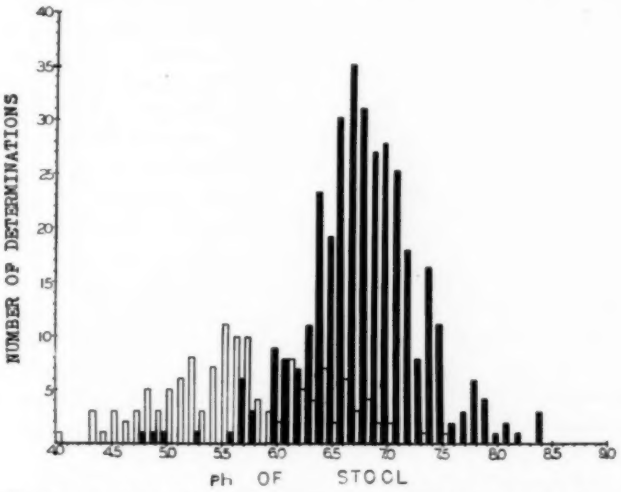


Fig. 7.—pH values on the stool. Black represents the infants fed cow's milk; white represents the breast-fed infants.

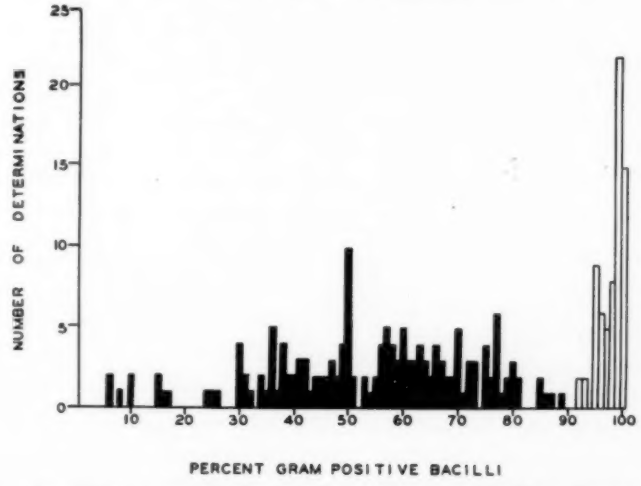


Fig. 8.—Percentage of gram-positive bacilli in the stool. Black represents stools of infants fed cow's milk; white represents stools of breast-fed infants.

milk, and only a slight rise in percentage was noticed in infants fed SMA 1. SMA 1 was the formula commercially available at the time of these investigations. In SMA 3 and SMA 5 changes were made in the fatty acid composition. Shorter chain saturated fatty acids of the series C_{10}-C_{14}, found to be inhibitory for Lactobacilli[7, 8] were reduced to lowest possible levels. SMA 3 and SMA 5 had identical composition with the slight difference of added B_{12} (0.25γ per cent) and trace of manganese (1 mg. Mn per cent) in SMA 5. The addition of B_{12} and manganese had no apparent effect on pH and bacterial composition of the stools.

Both SMA 3 and SMA 5 showed a distinct change over SMA 1 regarding pH and average percentage of gram-positive rods in the stool. pH of the stool of infants fed the SMA formulas with the modified fat formula was practically identical with that found in breast-fed infants. In appearance, the stools closely resembled "breast milk stools," in color, consistency, and in their lack of putrefactive odor. However, the gram-positive flora in the stool of infants fed SMA 3 or SMA 5 still lacked the uniformity of flora characteristic for the stools of normal breast-fed infants.

DISCUSSION

An easily discernible difference between infants of equally satisfactory nutritional state fed breast milk and the usual cow's milk formulas may be found by examination of the feces. The distinctly acid stool with its predominantly gram-positive flora in breast-fed infants differs from the less acid stool and mixed bacterial flora of the infants fed cow's milk.

Studies of the last few years on the nutritional value of intestinal antimicrobial agents[11-15] seem to indicate the importance of intestinal flora not only as the possible source of vitamin-like substances, but also as a harmful factor depriving the host of essential food constituents[16] or as the source of metabolites, interfering with growth and with the normal function of organs, in particular with that of the liver. These recent findings may shed new light on the nutritional importance of the predominantly bifidus flora in breast-fed infants, in contrast to the mixed intestinal flora in infants fed cow's milk formulas.

In this study, the results of pH determinations and percentage counts of the gram-positive bacilli found in stools of infants fed breast milk or the usual evaporated milk formulas agree closely with the findings of previous workers.[3, 16, 18]

The gram-positive bacilli seen in the smears of stools obtained from breast-fed infants and infants fed cow's milk are not necessarily *L. bifidus*. Studies in progress in this laboratory have shown that there may be present several straight rods as apparent mutants of *L. bifidus*,[8] and also bifid forms, which seem to differ in their nutritional requirements and in their metabolic products, from what we may call "true" *L. bifidus*. Thus, although *L. bifidus* may be cultured in almost equal numbers from the stools of breast-fed or bottle-fed infants,[19] the strains isolated are not necessarily identical.

The pH and bacterial flora of the feces represent only the last stage of a long sequence of microbiological reactions throughout the gastroin-

testinal tract. In infants, these consecutive phases have not yet been investigated.

The method for intubation of the infant's intestine has been previously used for treatment of cases with intestinal obstruction and was first suggested by Scheltema.[20] Intubation as a technique may introduce more or less serious sources of error in investigations. It probably stimulates motility, as indicated by the higher pH of the stools in some of the intubated breast-fed infants. Further, intubation may also influence the secretory processes in the intestine. However, this effect was apparently not very pronounced in these observations as demonstrated by the fact that the results obtained agree closely with those obtained in studies of the intestinal pH values of infants immediately after death.[21, 22, 23] The interference with normal sucking and the removal of the intestinal fluid both tend to produce dehydration, which clinically became apparent in two infants who developed a mild temperature elevation responding promptly to increased fluid intake.

The inaccuracy of counting bacteria in a stool smear, or in a hanging drop, as well as that of available methods for the quantitative culture of *L. bifidus* and other intestinal bacteria, should also be considered.

In the light of all these shortcomings and of the limited number of observations, it is necessary to consider the investigations and their results presented merely as pilot experiments. The conclusions drawn should serve only as indications for trends observed, and may be used only as a basis for more exact future studies with reference to experiments in vitro.

The following findings appear to be well documented: (1) The duodenum was relatively sterile. Bacteria, chiefly enterococci in small numbers, were found in the jejunum and ileum. (2) There was marked bacterial proliferation in the cecum and distal to it. (3) The pH of the intestinal contents reached an alkaline peak in the cecum. The finding that differences in pH and bacterial composition of the intestinal contents could not be demonstrated in the cecum and proximal to it, between breast-fed and cow's milk-fed infants, was unexpected and deserves to be emphasized. Distal from the cecum, differences became evident between the two groups of infants. In the breast-fed infants, the pH dropped gradually to a more acid level in the stool. This was in contrast to infants fed dilutions of evaporated milk, who showed either no changes or only a slight fall in pH in the same span of intestine.

The lowering of the pH in the presence of increasing Lactobacilli and decreasing organisms of other types suggest the Lactobacillus as a cause of the lowering of the pH. This is an assumption supported by the converse bacterial activity and relative lack of change in the pH in the infants fed cow's milk. The cultures of the intestinal contents demonstrated two points: (1) No *L. bifidus* was cultured proximal to the terminal ileum. (2) *L. bifidus* was cultured from the large bowel of both the breast milk-fed and cow's milk-fed infants with about equal incidence.

Acid produced by *L. bifidus* is generally related to fermentation of lactose. Studies on the growth requirements of *L. bifidus* have shown[24] that *L. bifidus* prefers lactose as source of carbohydrate. Its growth is not well supported by glucose, galactose, maltose, or sucrose. In contrast, straight

mutants of *L. bifidus* (*L. acidophilus*) do not discriminate between these various sugars. According to our findings obtained through intubation, reducing sugar, although in varying, often small, quantity, was found in the contents not only of the small but also of the large intestine in both breast-fed and cow's milk-fed infants.

The development of acid stool and bifidus flora in breast-fed infants was in the past generally attributed to the high lactose and low protein, low salt content of breast milk.[4, 5, 25] The same principle was followed in various attempts to adapt cow's milk to human milk for infant feeding.[25-27] Our observations with several brands of "adapted milk" brought no confirmation of this leading principle. The best results were obtained with a formula (modified SMA) in which a fat mixture was used with a low proportion of short chain saturated fatty acids found to be inhibitory for *L. bifidus*. With this formula the fecal pH was practically identical with that found in breast-fed infants. Although the average percentage of gram-positive rods in the stool of infants fed this formula was closer to that observed in the stool of breast-fed infants than seen after the use of any other available "adapted" milk, the uniform bifidus flora characteristic for the stool of normal breast-fed infants was not attained.

SUMMARY AND CONCLUSIONS

The pH and relative occurrence of gram-positive bacilli have been determined in the stools of 236 infants fed exclusively either human or cow's milk. The latter was given in the form of the usual formulas of evaporated milk or as commercial brands of "adapted" milk.

Fifteen infants fed breast milk or evaporated milk have been intubated with a double lumen Miller-Abbott tube. The pH and the proportion of gram-positive bacilli have been determined on specimens withdrawn from various levels of the intestine. On some, total bacterial counts, analyses for reducing sugar, and cultures for *L. bifidus* were performed.

1. In general, the duodenum was relatively sterile. Bacteria, mainly enterococci, were found in the jejunum, and in increasing numbers toward the ileum. There was marked bacterial proliferation in the cecum and distal to it.

2. The pH of the intestinal content reached a peak in the cecum around pH 7.0 to 8.0, and tended to fall in the distal portion of the colon. This change toward a distinctly acid level was more pronounced in breast-fed infants than in infants fed cow's milk.

3. Lactobacillus was never cultured above the terminal ileum, but was usually cultured in the large intestine of both breast-fed infants and infants fed cow's milk.

4. Reducing sugar in varying amounts was found in the intestinal content throughout the entire length of the intestinal tract of both breast-fed infants and infants fed cow's milk.

5. The average pH in the breast-fed infants was 5.5. In infants fed evaporated cow's milk modified with maltose-dextrin type sugar, the pH was 6.7.

6. The flora of the breast-fed infant's stool was comprised of over 90 per cent gram-positive bacilli. The stool of the infant on cow's milk was variable in its bacterial flora.

7. The feeding of brands of "adapted" milk failed to produce stools with an acidity and bacterial flora similar to those found in the stools of breast-

fed infants. Only a special modification of SMA approached the effect of breast milk on the fecal pH. However, even with this formula, the bacterial flora did not reach the uniformity found in the stools of breast-fed infants.

REFERENCES

1. Tissier, H.: Recherches sur la flore intestinale normale et pathologique du nourrisson, Paris, 1900.
2. Moro, E.: Ueber die nach Gramfärbbaren Bacillen des Säuglingsstuhles, Verläufige Mitteilung, Wien. klin. Wchnschr. **13**: 114, 1900.
3. Brown, E., and Bosworth, A. W.: Studies of Infant Feeding. XVI. A Bacteriological Study of the Feces and the Food of Normal Babies Receiving Breast Milk, Am. J. Dis. Child. **23**: 243, 1922.
4. Bessau, G., in Tobler-Bessau: Allgemeine path. Physiologie der Ernährung, etc., Wiesbaden, 1914.
5. György, P., in Pfaundler-Schlossmans Handbuch der Kinderheilkunde, vol. II, pp. 324 ff, 1931.
6. Norris, R. F., Flanders, Thelma, Tomarelli, R. M., and György, Paul: The Isolation and Cultivation of Lactobacillus Bifidus: a Comparison of Branched and Unbranched Strains, J. Bact. **60**: 681, 1950.
7. Tomarelli, R. M., Norris, R. F., Rose, C. S., and György, P.: The Effect of Fatty Acids on the Growth of Strains of L. Bifidus, J. Biol. Chem. **187**: 197, 1950.
8. Hassinen, J. B., Durbin, G. T., and Bernhart, F. W.: The Bacteriostatic Effect of Saturated Fatty Acids, Arch. Biochem. & Biophys. **31**: 183, 1951.
9. Teply, L. J., and Elvehjem, C. A.: Titrimetric Determinations of Lactobacillus Casei Factor and Folic Acid, J. Biol. Chem. **157**: 303, 1945.
10. Somogyi, M.: Protein-Free Filtrate for Blood Sugar and Blood Urea Nitrogen Determinations, J. Biol. Chem. **160**: 62, 1933.
11. Moore, P. R., Evenson, A., Luckey, T. D., McCoy, E., Elvehjem, C. A., and Hart, E. B.: Use of Sulfasuxidine, Streptothricin in Nutritional Studies With the Chick, J. Biol. Chem. **165**: 437, 1946.
12. György, P., Stokes, J., Jr., Smith, W. H., and Goldblatt, H.: Studies on the Use of Aureomycin in Hepatic Disease. II. The Effect of Aureomycin on Experimental Dietary Hepatic Necrosis, Am. J. M. Sc. **220**: 6, 1950.
13. Stokstad, E. L. R., and Jukes, T. H.: Further Observations on the "Animal Protein Factor," Proc. Soc. Exper. Biol. & Med. **73**: 523, 1950.
14. György, P., Stokes, J., Jr., Goldblatt, H., and Popper, H.: Antimicrobial Agents in the Prevention of Dietary Hepatic Injury (Necrosis, Cirrhosis) in Rats, J. Exper. Med. **93**: 513, 1951.
15. Nesheim, R. D., and Johnson, O. C.: Response of Pigs to Streptomycin, Proc. Soc. Exper. Biol. & Med. **75**: 709, 1950.
16. de la Huerga, J., and Popper, H.: Urinary Excretion of Choline Metabolites Following Choline Administration in Normals and Patients With Hepatobiliary Diseases, J. Clin. Investigation **30**: 462, 1951.
17. Darlancourt, H., and Lavanden, R.: pH in Stools of Normal and Sick Infants, Nourrisson **19**: 147, 1931.
18. Gerstley, J. R., Howell, K. M., and Nagel, B. R.: Some Factors Influencing the Fecal Flora of Infants, Am. J. Dis. Child. **43**: 555, 1932.
19. Olsen, E.: Studies on the Intestinal Flora of Infants, Copenhagen, 1949.
20. Scheltema, G.: Permeation in the Examination and Treatment of the Stomach and Intestines, Arch. Roentg. Ray., Lond. **13**: 144, 1908-09.
21. Moro, E.: Morphologisch und biologische Untersuchungen über die Darmbakterien des Säuglings, Jahrb. f. Kinderh. **61**: 685; 870, 1905.
22. Tissier, H.: Reapparition des microbes dans l'intestin du nourrisson, Ann. Inst. Pasteur **19**: 109, 1905.
23. Goeters, W.: Lactic and Flora Occurring in Small Intestines of Nurslings, Arch. f. Kinderh. **83**: 83, 1940.
24. Rose, Catharine S., Poster, E. K., Avery, A., Norris, R. F., and György, P.: The Effect of Mono- and Disaccharides on the Growth of L. Bifidus and Its Mutants With Observations on the Toxicity of Autoclaved Cystine, J. Bact. In press.
25. Bessau, G.: Zum Problem der künstlichen Ernährung des Säuglings, Deutsche med. Wchnschr. **64**: 397, 1938.
26. Gerstenberger, H. J., Haskins, H. D., McGregor, H. H., and Ruh, H. O.: Studies in the Adaptation of an Artificial Food to Human Milk, Am. J. Dis. Child. **10**: 249, 1915.
27. Gerstenberger, H. J., and Ruh, H. O.: Studies in the Adaptation of an Artificial Food to Human Milk. II. A Report of Three Years Clinical Experience With the Feeding of SMA: Reports of the Section of Diseases of Children of the A. M. A., p. 137, 1918.

SOME SPECIAL PROBLEMS IN THE USE OF ACTH AND CORTISONE THERAPY IN CHILDREN

A Report of Three Cases

Reginald Wilson, B.A., M.D., F.R.C.P.(C), and
Richard Rowe, M.B.(N.Z.), M.R.C.P.(Ed)
Vancouver, B. C.

INTRODUCTION

ACTH and cortisone are now in widespread use in a variety of disorders of children and adults. While certain side actions of these hormones have been encountered already as a result of such treatment, the full extent of the associated metabolic effects is not yet firmly established—especially is this so in the pediatric age group. Until the necessary accumulation of case reports is achieved over a period of years the complete assessment of the unusual and dangerous as well as the beneficial effects of these substances will not be possible.

MATERIAL

We have treated a limited number of children with ACTH and cortisone in the Paediatric Department of the Vancouver General Hospital. In the present report the cases of three patients will be described in whom we have encountered an unusual and unexpected side effect. These are:

(1) A boy who had nephritis with edema. He died from pulmonary embolism.

(2) A girl with dermatomyositis who developed marked alteration in blood lipids.

(3) A girl with alopecia totalis in whom there was prolonged impairment of sugar tolerance while having ACTH therapy.

From the Pediatric Wards and the Metabolism Unit, Vancouver General Hospital.

DOSAGE

The exact dosage of ACTH and cortisone for pediatric patients at different ages is unknown. In each case dosage must be individualized. The accompanying Table I and comments on control of dosage illustrate the principles which guided us in treating these patients.

Thorn Test.—In doing the Thorn test in children an immediate dosage of 25 mg. of ACTH was used in all patients except infants under 2 years, in which case 10 mg. was used.

CONTROL OF DOSAGE

With ACTH an adequate dose was considered to be that amount which reduced the number of circulating eosinophils to zero on near zero figures. If this did not occur after a few days on the starting dose the amount was usually increased until the desired fall was obtained. Overdosage was revealed by signs of intolerance such as sudden increase in body weight, development of edema, hypertension, fall in urinary output, reduction in urinary chlorides and serum potassium. Toxic effects were sometimes heralded by the development of moon facies and acne, though in themselves these were not considered as indications for stopping therapy. With cortisone, an effective dosage was found to be about twice that of ACTH. A reduction in circulating eosinophils was not considered necessary for an effective dosage with cortisone. With

this drug the dosage was increased until a satisfactory clinical response was obtained or toxic signs intervened. These signs were similar to those observed in ACTH therapy.

Table I. Starting Dosage (Per Twenty-four Hours) of ACTH and Cortisone for Children

AGE (YR.)	ACTH
0- 1	10 mg. given by i.m. injection in 4 doses of 2.5 mg. q.6.h.
1- 5	20 mg. given by i.m. injection in 4 doses of 5 mg. q.6.h.
5-10	40 mg. given by i.m. injection in 4 doses of 10 mg. q.6.h.
10-15	60 to 100 mg. given by i.m. injection in 4 doses of 15 to 25 mg. q.6.h.
	CORTISONE
0- 1	20 mg. given by i.m. injection in 1 total dose daily
1- 5	40 mg. given by i.m. injection in 1 total dose daily
5-10	80 mg. given by i.m. injection in 1 total dose daily
10-15	100 to 200 mg. given by i.m. injection in 1 total dose daily.

CASE REPORTS

Case 1.—P. L., white male, aged 2½ years. Nephritis with edema.

History.—This boy was admitted to hospital June 15, 1950, with generalized edema. Three months before, he had suffered an exanthema which was possibly scarlet fever. Three weeks after this infection, he developed edema of the face and abdomen and proteinuria was discovered. Subsequently this edema fluctuated until anasarca of an incapacitating degree finally forced his admission.

Physical examination revealed massive edema of the body. Blood pressure was 118/77, and he was afebrile.

During the first two weeks in hospital he received no specific therapy apart from a low-salt diet. Daily fluid intake varied between 800 and 1,000 ml. but the urine output was considerably less. The edema spread rapidly to involve the penis and scrotum. Excoriation of the skin in the perineum became a problem.

Laboratory Findings.—Urine specific gravity varied between 1.015 and 1.030. Urine contained +4 protein, +2 white blood cells, and occasional hyaline casts but no red cells. Examination of the blood showed no anemia, eosinophilia of 12 per cent, and erythrocyte sedimentation rate of 115 mm. per hour. Total blood protein was 4.5 grams per cent (albumen 2.7 grams per cent, globulin 1.8 grams per cent). The blood cholesterol was 816 mg. per cent, and the nonprotein nitrogen 25 mg. per cent.

Progress.—Cortisone, 40 mg., was administered daily for thirteen days. Collection of the total urinary output was facilitated by the use of a metabolic bed. During the first week of therapy he was in fluid imbalance with an average daily intake of 800 ml. and a urinary output of 250 ml. His weight increased by one pound. Edema spread to the anal region and he developed rectal prolapse which became very tender and excoriated. During the second week there was a mild diuresis and his fluid excretion equalled or surpassed the intake. This improvement was short-lived and the urinary output fell sharply again. In view of the evidence of fluid retention together with the sudden reduction in urinary chlorides and slight rise in serum potassium, it was decided to discontinue cortisone. Hemoglobin which had fallen to 11.1 grams at the beginning of treatment fell further to 7.7 grams. The total serum cholesterol which had fallen to 692 mg. per cent continued to fall and measured only 450 mg. per cent at the end of treatment. During the last four days of cortisone therapy rectal temperature fluctuated between 99° and 100.5° F. On cessation of cortisone his condition rapidly dete-

riorated, and his temperature rose immediately reaching 103° F. The respiratory rate remained unchanged. The fever failed to respond to antibiotic therapy. An erysipelatoid lesion spread from the perianal area to involve the lower extremities which became extremely tender. White cell count rose to 26,000 per cubic millimeter and red cells appeared in the urine. Terminally the stools became loose and tarry and the respirations rapid and shallow. He died eleven days after cessation of cortisone.

Autopsy.—An ante-mortem thrombus extended from the right iliac vein to 1 cm. above the renal veins. There was thrombus in both renal veins and the pulmonary artery was full and clotted. The lungs showed numerous areas of infarction particularly in the right lower lobe; both kidneys were enlarged, very pale, and had a smooth surface. The cut surface showed gross increase in thickness of the cortex. The medulla appeared swollen. On microscopic examination there was marked tubular degeneration, and although there was no crescent formation in the glomeruli, many of these appeared tufted and all showed increased cellularity.

Comments.—While a lack of systemic response to infection under cortisone treatment was seen in this boy, the main interest lies in the thromboembolic phenomena which were responsible for this death. Several factors are probably involved in this. First, the metabolic bed on which the patient was nursed and which facilitated the collection of urine and feces undoubtedly decreased the normal amount of movement of the body in general and lower limbs in particular. Second, an infection was evident in the legs. Third, a further possibility is that of side effect of cortisone. Cosgriff and associates[1] have shown in a small series that 80 per cent of adult patients under treatment with ACTH and cortisone have increased coagulability of the blood lasting as long as fifteen days after treatment was stopped. The effect was more noticeable, dose for dose, with ACTH than with cortisone and there appeared to be a definite relation quantitatively to the amount given. They felt that a combination of factors such as immobility, infection, and shortened coagulation time as from cortisone therapy might well summate to precipitate thrombosis. In our patient there was probably a similar combination of circumstances, and Cosgriff's theory makes an attractive explanation for this incident. It certainly raises the question as to whether anticoagulation therapy should be administered in individual patients under treatment with these hormones as was proposed by Cosgriff. It suggests also that we should avoid all factors which immobilize young children during treatment with these substances.

CASE 2.—F. W., White female, aged 9 years. Dermatomyositis.

History.—In late October, 1949, this girl developed malaise, anorexia, stiffness of the knees, and weakness, most marked in the legs. One week later she appeared pale, there was swelling around the eyes and of the knees and ankles, and her leg and arm muscles were tender. By January, 1950, three months later, she had become completely bed-ridden with these symptoms but for some weeks prior to this date she had been able to walk from her bed only as far as the bathroom. The erythrocyte sedimentation rate rose early in the disease.

Physical examination on admission in June, 1950, revealed a pale girl with a temperature of ½° to 1° F. above normal. Around both eyes there was a purplish erythema with swelling of the lids. There was a brawny induration of all subcutaneous tissues with dry scaliness visible on the lower cheeks around the mouth and over the exten-

sor surfaces of the forearms below the elbows. On the skin over the nail bases visible capillary loops were present. No abnormal neurological signs were discovered. There was limitation of extension of both elbows and flexion of both knees and ankles. She was unable to turn over in bed or lift her head from the pillow because of the weakness involving all muscle groups. No fibrillation of muscle was noted. There was no lymph node enlargement nor were the spleen and liver enlarged. No heart murmur or cardiac enlargement was discovered. The clinical diagnosis of dermatomyositis was supported by skin and muscle biopsy.

Laboratory Findings.—The findings were as follows: erythrocyte sedimentation rate 115 mm. per hour; serum calcium 9.3 mg. per cent; total protein 6.16 grams per cent; nonprotein nitrogen 27 mg. per cent; uric acid 5.8 mg. per cent; alkaline phosphatase 5 King Armstrong units; Serum sodium 325 mg. per cent; cholesterol 166 mg. per cent; phosphorus 4.8 mg. per cent. Hemogram was normal apart from slight normocytic anemia. There were no lupus erythematosus cells in the marrow. Cerebrospinal fluid was normal; electrocardiogram, normal; urinary creatine 0.20 Gm. in twenty-four hours.

Progress.—For one month beginning June 22, 1950, cortisone was given in a dose of 100 mg. daily. There was immediate improvement in the muscle weakness so that she was able to lift her head for short periods and move in bed a little. Her sense of well-being was restored and there was less brawny induration of subcutaneous tissues, but after one month progress was stationary. Contracture of joints was only slightly less noticeable and weakness was still profound. Erythrocyte sedimentation rate and urinary creatine excretion remained very high (0.5 Gm. in twenty-four hours).

From July 23, 1950, after one month, the dosage of cortisone was increased to 150 mg. daily. On the third day of the new dosage methyl testosterone was added in a dosage of 50 mg. daily in an attempt to promote protein anabolism. Soon afterward she showed early signs of cortisone intoxication which became worse in the next three days. Her pulse became very rapid, cardiac action was tumultuous, she suddenly gained weight, urinary output and chlorides fell sharply, and doughy swelling of the abdomen appeared. In view of these adverse signs all medications were discontinued on July 29. Subsequently her general condition continued to decline with continuation and aggravation of the above-mentioned signs. By August 10, she was in extremis. The blood serum showed the creamy consistency seen in hyperlipemia. The blood cholesterol had risen from 166 to 640 mg. per cent. At this time she was given aqueous extract of adrenal cortex in doses of 50 c.c. intravenously daily for two days. In the next few days her condition improved. Urinary output increased strikingly, her weight fell, the skin rash which had been aggravated began to subside, and her biochemical findings began to return to normal. Abdominal swelling and tachycardia subsided although this latter change was much more gradual. Despite this symptomatic improvement there was no really satisfactory change in the basic disease process.

In view of the poor response to cortisone it was decided to treat her with ACTH. After a rest period of six weeks she was started on ACTH in a dosage of 40 to 60 mg. daily, by intramuscular injection, for a period of one month. Soon after beginning this treatment she again improved. She could sustain her head against gravity and could lift both legs from the bed. She was able to roll over and make some attempt to kneel. However, after three weeks' treatment, hirsutism and abdominal distention developed and there was paronychial infection of both great toes. At this time tachycardia was aggravated and the *lipemic serum reappeared;* this time, however, blood cholesterol was only 200 mg. per cent.

On October 21, muscle biopsy showed no improvement. Since October 16, she

had continued without adrenal hormone therapy. The urinary creatine is 0.4 Gm. for twenty-four hours. Her disease is still active (erythrocyte sedimentation rate 110 mm. per hour) but in a subacute phase, and her general condition and muscle power are better than before treatment. The lipemia gradually subsided after cessation of ACTH therapy. Physiotherapy was given during the course of her hospital stay except at times when she was too ill to tolerate this.

Recent follow-up examination reveals a persistent weakness and atrophy of muscles with mild generalized calcinosis.

Comments.—The unusual finding here was the alteration in the blood lipids. Aldersberg and collaborators[2] have found that cortisone and ACTH produced an elevation of blood cholesterol levels in 77 per cent of forty-seven courses of treatment. This effect was more marked with cortisone than with ACTH and was especially liable to occur with longer courses of treatment. In their hypercholesterolemic group, figures exceeding 280 mg. per cent constitued some 36 per cent of the abnormal cases. In these responses this girl's findings are consistent with this published work. The hyperlipemia which occurred twice in this child was an unexpected phenomenon and for it we have no adequate explanation. In recent studies[3, 4, 5] a marked lipemia with fatty infiltration of the liver has been recorded during the administration of cortisone to experimental animals.

Archer[6] has briefly summarized the available literature relating to the pituitary and adrenal mechanism and fat metabolism in animal experiments. He predicted that fatty infiltration of the liver would be found as a result of ACTH and cortisone treatment in man. While lipemia has been thought to develop as a result of the effect of the hormone directly on fat metabolism or secondarily to its effect on carbohydrate metabolism, it may be that there is some distinctive alteration in the metabolism in certain diseases which predisposes to the development of this complication during treatment with these agents. For example, the disease dermatomyositis is characterized by some of the phenomena of hypersensitivity. Arnold Rich[5, 7] has shown in animal experiments that the development of hyperlipemia under cortisone treatment is contingent upon previously making the animals hypersensitive. Kobernick and More[3] have also shown that the development of hyperlipemia in rabbits is contingent upon previous conditioning of the animals with cold. It seems possible that the abnormalities of the fat metabolism which developed under treatment with cortisone in this case was due to some alteration in her metabolism akin to the hypersensitivity produced by Rich which predisposes to the development of hyperlipemia in animals.

In Case 1 of the present report, a child with nephritis and a high blood cholesterol, the tendency under cortisone treatment was toward a lowering of the cholesterol. This also seems to support the view that there is some peculiarity of the metabolism in a disease such as dermatomyositis which predisposes to hyperlipemia.

Case 3.—D. B., white female, aged 10 years. Alopecia universalis.

History.—This girl is an allergic subject and has suffered from asthma and eczema most of her life. In other respects she was perfectly well until January, 1948, when she developed a patchy baldness for no apparent reason. This progressed rapidly until

in three months' time she had suffered a complete loss of hair including that of the body, scalp, and eyebrows. In July, six months after the onset of her symptoms, she was started on ACTH therapy, 60 mg. daily. This was continued in varying dosage for two months by which time she had received 3,315 mg. ACTH. During this interval she had developed a very encouraging growth of hair on her scalp and quite heavy growth of eyebrows. She did, however, show various side effects, such as obesity, moon facies, buffalo hump, and acne. There was also a slight generalized growth of body hair, including the face.

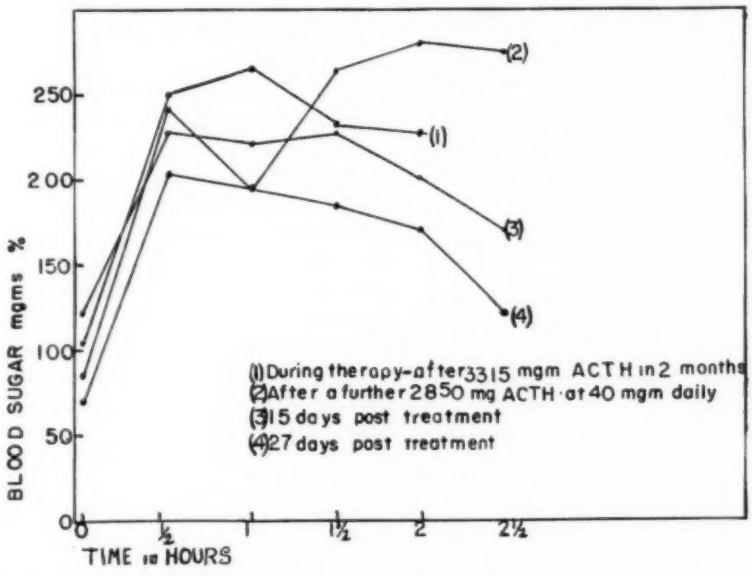


Fig. 1.—Glucose tolerance curves during and after therapy with ACTH for alopecia totalis.

At this time and while on a daily dose of 100 mg. of ACTH she began to show 2 to 4 ++ glucose in the urine. Her blood sugar curve (Fig. 1, Curve 1) showed impaired tolerance. Dosage was reduced to 40 mg. daily and on this dose the fasting sugar remained normal and glycosuria was absent. However, a second sugar tolerance curve (Fig. 1, Curve 2) done after a total dosage of 6,165 mg. still showed an abnormal sugar tolerance. During this interval no ketosis was present and single fasting sugar determinations were frequently normal. When ACTH was stopped her sugar tolerance gradually improved (Fig. 1, Curves 3 and 4), and finally had returned to normal in two months.

The hair growth which had been very satisfactory during treatment stopped immediately with cessation of therapy. Soon the hair lost its lustre and began to fall out again. Follow-up examination two months later revealed complete relapse of her alopecia and almost complete disappearance of the previously noted side effects.

Comments.—The disturbance of carbohydrate metabolism which occurs during treatment with ACTH has been frequently reported by others. Wilder has pointed out that it differs from true diabetes mellitus in several respects, including the following:

(1) It is insulin resistant.

(2) It is accompanied by azotemia.

(3) It responds to fasting more promptly than it does in a truly diabetic subject.

(4) It is usually accompanied by other evidence of adrenocortical hyperfunction.

In our patient the impaired glucose tolerance followed such a pattern and appeared to be a completely benign affair. It is interesting to note that this was the only patient so affected in a series of twenty-seven patients receiving ACTH for periods over one month and also that it was this patient who more than any other in the series showed other signs of adrenocortical hyperfunction such as moon facies, obesity, and buffalo hump. The temporary remission of her alopecia is receiving further study.

DISCUSSION

There are innumerable physiological side effects associated with the use of ACTH and cortisone. These have frequently been described in the literature and are mainly grouped as to their effects on water and electrolyte metabolism. However, there are also many less prominent side effects, such as possible deleterious effect on wound healing, disturbances of glucose tolerance, a tendency to masking of the usual signs of inflammatory reaction, an inhibition of the customary signs of atopy, and possible stimulation of the activity of latent tuberculous disease. The latter effects are not well understood, nor is there sufficient information concerning them from reported experience in children's diseases.

With one exception in our limited general experience with the use in these hormones in children we have not had serious or permanent deleterious results from side effects or complications. Case 1 is the exception, but in this instance there were conditions which predisposed to the complication which developed. In a similar way care must be taken to avoid the dangers of potassium deprivation under circumstances where the metabolism of that element is likely to be disturbed. Although we have used ACTH for long periods and in maximum dosage we have not yet noted a progressive or malignant hypertensive effect in children. From one experience on adult wards of this hospital we have been warned regarding this danger and we know that it has happened elsewhere in children. This complication should be guarded against by the meticulous daily observation of blood pressure of children under treatment with ACTH and the drug should be stopped if there is any consistent rise in blood pressure.

Delayed clearing of casual infection has been noted in our patients. However, we have not encountered difficulty with healing after surgery or biopsy in four instances in children under treatment with these hormones.

As our knowledge of these less common side effects is still meager especially in children, it should be increased wherever possible by recorded clinical observation. The present report serves to record some new experience in this field and gives documentary evidence regarding three such effects. It also emphasizes the difficulty of assessing the clinical value of a new therapeutic agent until the nature and the extent of the various side effects are fully understood.

SUMMARY

1. Three cases are reported which illustrate some noteworthy responses

encountered during the use of ACTH and cortisone in children.

2. A case of nephritis with edema demonstrated the tendency to intravascular clotting while under treatment with cortisone. Emphasis should be placed on this case because of its fatal outcome.

3. In a case of dermatomyositis some symptomatic relief was obtained with the use of ACTH and cortisone, but therapy was hindered by the development of hyperlipemia during this treatment. The development of this complication is thought to be related to some peculiarity of the metabolism of the disease under treatment. ACTH and cortisone did not stop the characteristic progress of this disease.

4. Prolonged dosage with ACTH in a child caused a temporary and benign impairment of glucose tolerance.

5. Some implications of the reported side effects from the use of ACTH and cortisone in children are discussed.

We wish to express our gratitude for the helpful advice and criticism of Dr. Russell Palmer, Chairman, and the members of the Metabolism Committee of the Vancouver General Hospital. The ACTH and cortisone was supplied by the National Research Council of Canada.

REFERENCES

1. Cosgriff, S. W., Diefenbach, A. F., and Vogt, William, Jr.: Am. J. Med. **9**: 752, 1950.
2. Aldersberg, D., Schaeffer, L., and Drachman, S. R.: J. A. M. A. **144**: 909, 1950.
3. Kobernick, S. D., and More, R. H.: Proc. Soc. Exper. Biol. & Med. **74**: 602, 1950.
4. Salag, Amira A., Borasi, M., and Cavallero, C.: Lancet **1**: 641, 1951.
5. Rich, A. R., Cochran, T. H., and McGoon, D. C.: Bull. J. Hopkins Hosp. **88**: 101, 1951.
6. Archer, B. H.: J. A. M. A. **143**: 570, 1950.
7. Editorial: Lancet **2**: 541, 1950.

LATENT HEMOLYTIC DISEASE OF THE NEWBORN INFANT

The Variable Quantitative Relationship Between the Amount of Maternal Rh Antibodies and the Extent of Damage to the Rh-Positive Infant

Joseph Grundorfer, M.D.
Newark, N. J.

A DECADE ago, a great contribution had been made to the science of medicine, when the Rh antigen was recognized as the cause of hemolytic transfusion reactions and an incompatibility of this blood factor was demonstrated as the cause of hemolytic disease of the newborn infant.

This discovery provided an etiology of two apparently isolated phenomena of great clinical significance. The interest in blood groups and hemagglutinins as a cause of disease had been, once more, greatly stimulated; however, many problems on the subject of hemolytic disease in the newborn infant remained unsolved.

Among the numerous papers which appeared in the literature, the question had repeatedly been raised why an Rh-positive infant who exhibits little or no clinically demonstrable evidence of hemolytic disease, may be born to an Rh-negative woman who has shown considerable amounts of Rh antibodies in her serum during pregnancy.

Dockeray and Sachs[1] found among sixty-one women, three whose sera contained Rh antibodies. The children were reported normal though no hematological data had been given. They concluded that Rh antibodies pass the placental barrier only in certain conditions which may change during the course of pregnancy. Goldbloom and Lubinski[2] observed one case. Rh antibodies were present at time of delivery, but clinical or laboratory evidence of hemolytic disease could not be found. Greatly varying amounts of antibodies which go through the placenta to the fetus is offered by them as the cause without any further explanation. Kariher and Miller[3] furnished some data on prenatal antibody studies in two cases and thus tried to prove that maternal isoimmunization is relatively more frequent than the incidence of disease in the offspring. Carter[4] reported four cases of maternal sensitization with an Rh-positive infant who appeared normal on clinical and hematological examination. Two cases of Rh isoimmunization were reported by Donohue and Fremes.[5] In each case, the mother first gave birth to an infant afflicted with hemolytic disease and in a subsequent pregnancy delivered a clinically normal baby. In one case, they explained the normality of the infant with a maternal antibody response to weak antigens and concluded that "the titer is not a reliable index of the amount of damage antibodies may cause." Howard and associates[6] reported four cases of normal Rh-positive infants born to mothers with laboratory evidence of Rh sensitization. They interpreted the phenomena of these cases by offering the hypothesis of the an-

From the Rh Center and Department of Laboratories at Newark Beth Israel Hospital.

amnestic rise of nonspecific antibodies and that of the protective effect of specific subgroup blocking antibodies.

That isoimmunization is not necessarily synonymous with the occurrence of hemolytic disease in the offspring and the maternal antibody titer has to reach a certain degree sufficient to produce disease in the infant, had also been emphasized by Sacks, Kuhns, and Jahn.[7] They reported a series of seventy-nine sensitized Rh-negative women; fifty-three delivered infants with hemolytic disease while twenty-six showed no evidence of disease. Their report, however, did apparently not exclude those Rh-negative infants born to mothers who carried antibodies as a result of some previous stimulation, and as there is no reason to doubt the normality of such infants, it would have been of great interest to learn how many of those twenty-six infants were found Rh positive.

Fifty-eight cases of Rh sensitization, completely followed through, had been seen during the first three-year period of this laboratory.[8] In seven instances, the mother delivered a normal infant, two of which were found to be Rh negative, and another three women had infants without much clinical evidence of hemolytic disease except for a very faint jaundice. The majority of these latter cases showed low-titered agglutinating maternal antibodies while only two revealed blocking antibody titers of one and three units in strength, respectively. From these observations the opinion was expressed that the production of antibodies may be initiated too late in many pregnancies in order to result in a significant disease of the infant.

The detection of these types of cases has certainly been greatly improved since the establishment of central laboratories which offer a service of periodic prenatal antibody studies; hemolytic disease of the newborn infant with absence of easily discernible clinical manifestations is, therefore, now recognized more frequently. However, the problem of Rh isoimmunization still remains rather puzzling especially in regard to the little progress achieved in the interpretation of the quantitative relationship between maternal antibodies and the extent of damage to the Rh-positive fetus of a sensitized Rh-negative mother.

This statement can be supported by an illustration of three cases which were recently investigated at this laboratory. In each case, an apparently normal infant was born to a mother who showed pronounced laboratory evidence of Rh sensitization. The early initiation of the maternal antibody titer and its constant rise throughout the entire second and third trimester of pregnancy, yet the unexpectedly satisfactory clinical condition of the newborn infant, are the outstanding features of this presentation.

CASE REPORTS

CASE 1.—Mrs. M. E., 28 years old, white, five years married, a para i, gravida ii, delivered in 1947, a full-term, normal infant. In 1950, when she became pregnant again, a prenatal Rh test was performed on her and her husband. The results were as follows:

Mrs. M. E.: Group A, Rh negative (cde); Rh antibodies not present (at 12 weeks of gestation); Mr. M. E.: Group O, Rh positive, Rh_1 hr′ (CDe/CDe).

At 19 weeks of gestation, evidence of sensitization could be established; an Rh antibody of 2 units in strength could be elicited in saline and albumin-plasma media.

Table I illustrates this antibody as it appeared during the course of this pregnancy. Its slow but steady rise with some decline toward term, its moderate but definite discrepancy as to its behavior in saline and albumin-plasma media is well visualized by the frequent titer determinations. The coating property of this antibody could be easily evidenced by the anti-human globulin test. The specificity was anti-Rh_o (anti-D).

TABLE I

WEEKS OF GESTATION	SALINE	ALBUMIN-PLASMA	ANTI-HUMAN-GLOBULIN
19	2	2	—
22	4	4	—
25	2	8	—
28	2	8	16
34	4	32	128
36	8	64	256
37	16	128	512
38	32	64	256
40	32	32	128

On Oct. 18, 1950, she spontaneously delivered a full-term, male infant who was well developed and weighed 8 pounds, 12 ounces. The infant appeared vigorous and had a lusty cry. Some pallor, but no jaundice could be noticed. Liver and spleen were not enlarged.

The baby was Group A, Rh positive, Rh_1 HR′ (CDe/cde). The direct antihuman globulin test (Coombs' test) was strong positive (4 plus). The cord serum revealed the presence of maternal Rh antibodies of 32 units in strength when demonstrated by the albumin-plasma method, and 128 units by the antihuman globulin test.

Immediately after birth the baby had 5,540,000 red cells and a hemoglobin of 132 per cent. There was no deviation of these findings on the following days. On October 19, the baby had 5,410,000 red cells (hemoglobin 114 per cent), and on October 20, 5,630,000 red cells (hemoglobin 112 per cent). Slight jaundice was noticed for the next three consecutive days. On October 22, the red cell count was 5,620,000 (hemoglobin 122 per cent); however, the direct antihuman globulin test still showed a strong positive reaction (4 plus). The next four hospital days also appeared uneventful, and on October 26, the baby was discharged with the following hematological findings; 5,270,000 red cells; hemoglobin 106 per cent; 11,400 white cells; polymorphonuclear leucocytes 26 per cent; lymphocytes 62 per cent; monocytes 2 per cent; eosinophils 4 per cent; stab cells 5 per cent; myelocytes 1 per cent; and absence of normoblasts.

After eight weeks, on December 11, the infant was seen again and presented the picture of a healthy infant with the following hematological findings considered normal for this age period: 4,500,000 red cells, hemoglobin 82 per cent. The direct antihuman globulin test still was positive (2 plus).

CASE 2.—Mrs. C. K., 23 years old, white, five years married, a para i, gravida ii, had in 1947 an uneventful delivery. At that time she was found Group O, Rh negative (cde), while her husband appeared to be Group A, Rh positive Rh_1Rh_2 (CDE). Rh antibodies could not be detected in her serum.

Late in 1950, when seen again at 20 weeks of gestation, her serum revealed an agglutinating (saline) antibody of 32 units in strength. Blocking or coating qualities could not be established at that time. Later on, an appreciable rise in titer could be noticed in those tests performed in an albumin-plasma medium; its coating character was now easily demonstrable by the antihuman-globulin technique. The performance of a blocking test always remained an extremely difficult problem. However, the existence of blocking antibodies could not be denied in the presence of the considerably high titers (with albumin-plasma and antihuman-globulin) found late in the pregnancy. The specificity of this antibody was anti-Rh_o (anti-D). Table II presents the various titer

TABLE II

WEEKS OF GESTATION	SALINE	ALBUMIN-PLASMA	ANTI-HUMAN-GLOBULIN
20	32	32	—
23	32	128	—
27	64	128	512
31	128	512	1024
33	128	512	2048
35	128	512	2048
37	1024	4096	8192

findings during the course of this pregnancy.

At 37 weeks of gestation she spontaneously delivered a male infant who appeared well developed and weighed 6 pounds, 3 ounces. The condition was good, the cry healthy. There was noticeable a very faint icterus twenty-four hours after birth; however, no pallor or edema. Liver and spleen were not enlarged.

The baby was Group A, Rh positive, Rh_2 HR″ (cDE/cDe). The direct antihuman globulin test was strong positive (4 plus). The cord serum revealed maternal Rh antibodies of 32 units in strength by the albumin-plasma, and 128 units by the antihuman globulin technique. Table III gives a list of hematological findings on the infant at birth and on the successive days.

TABLE III

TIME AFTER BIRTH	NUMBER OF RED CELLS	HEMOGLOBIN IN PER CENT
1 hour	6,140,000	104
6 hours	5,410,000	106
24 hours	4,990,000	112
3 days	4,760,000	103
4 days	4,340,000	96
6 days	3,220,000	73
8 days	4,390,000	92

The differential counts never revealed any unusual findings. There was always absence of normoblasts. The antihuman globulin test still gave a strong 4 plus reaction on the fifth day.

There appeared no change in the general behavior of the infant. When on the sixth day the red cell count and hemoglobin dropped to a considerably low level, it was decided to transfuse the baby. Sixty cubic centimeters of Group O, Rh-negative blood were administered by fontanel which were well tolerated, and the infant was discharged on the eleventh day. The attending pediatrician who saw the baby afterward in his office could not relate anything unusual in the further development of this infant.

At the age of 4 weeks the antihuman globulin test still gave a strong 3 plus reaction; the red cell count was 3,000,000; the hemoglobin 60 per cent.

CASE 3.—Mrs. A. H. 29 years old, white, a para i, gravida ii, delivered a normal infant several years ago.

In October, 1950, early in her second pregnancy, she was found Group A, Rh negative (cde), her husband Group A, Rh positive, Rh_1 HR′ (CDe/cDe). At 10 weeks of gestation her serum contained an agglutinating Rh antibody of 2 units in strength.

During the course of the pregnancy this antibody maintained its agglutinating quality; titer determinations in saline and albumin-plasma media yielded identical figures, and tests with the antihuman globulin reagent did not essentially reveal any coating tendencies of this antibody (Table IV). The specificity was anti-Rh_0 (anti-D).

TABLE IV

WEEKS OF GESTATION	SALINE	ALBUMIN-PLASMA
10	2	4
26	32	64
28	32	32
30	256	256
34	256	256
36	512	512
40	1024	1024

On May 6, 1951, she spontaneously delivered a full-term, well-developed male infant weighing 8 pounds, 3 ounces. There was no appreciable jaundice or pallor, and neither hepatomegaly nor splenomegaly was apparent. The baby progressed normally and left the hospital with the mother.

The infant was Group A, Rh positive, Rh_1 HR′ (CDe/cDe). The direct antihuman globulin test (Coombs' test) was performed at birth, after 5 days and 2 weeks, and, each time, invariably yielded a 2 plus reaction. The cord serum contained maternal Rh agglutinins demonstrable by the albumin-plasma method (1 unit) and the antihuman globulin technique (4 units).

Table V gives the hematological data.

TABLE V

TIME AFTER BIRTH	RED CELL COUNT	HEMOGLOBIN IN PER CENT
1 hour	5,180,000	112
24 hours	4,980,000	98
3 days	4,980,000	100
4 days	4,660,000	99
5 days	4,990,000	91
8 days	4,000,000	86
2 weeks	3,000,000	70
3 weeks	2,940,000	50
4 weeks	3,110,000	60

The number of white blood cells varied between 9,000 and 14,400. During the first week of life, the blood smears predominantly showed polymorphonuclear leucocytes; later on, this picture was followed by a pronounced lymphocytosis. One or two normoblasts (per 100 white cells) could occasionally be noted in some of the blood smears.

In spite of the excellent general progress, the baby showed, when 3 weeks of age, some pallor which could be directly correlated with the alarmingly low level of red cells and hemoglobin (Table V). The infant had, therefore, to be transfused. One hundred cubic centimeters of Group A, Rh-negative blood were administered intravenously. When 8 weeks old, the baby was seen again, and showed the following hematological findings: 4,800,000 red cells, hemoglobin 78 per cent; white and differential counts appeared normal. The antihuman globulin test, however, still gave a somehow positive result. Since then, the infant appears to be doing well.

DISCUSSION

These three reported cases show that one cannot with certainty predict the type of fetal disease by the nature (quality) and titer (quantity) of prenatal maternal antibodies beyond a general statement.

They present another exception to the commonly spread assumption that a high concentration of antibodies is an invariable precursor of hemolytic disease. Cases like those described prove that severe isoimmunization of the mother does not necessarily include severe or fatal disease in the offspring.

The morbid anatomy of hemolytic disease indicates that a long-range prenatal damage to the fetal hematopoietic system and vital organs exists and that the effect presumably arising during or after birth has only to be regarded as negligible.

The question is, therefore, brought forward as to the factors involved which eventually may cause such favorable variations in the development of an Rh-positive infant—due to a peculiar reaction to the maternal immune agglutinin.

It is well known, today, that the antigenic power of the Rh factor is subject to great variations. The antigen usually involved is D. Other antigens, like C, E, c, eventually may become responsible for the disease; however, D is the most frequent cause.

Several pregnancies or multiple blood transfusions are sometimes necessary to build up potent antibodies for the development of a severe reaction, while in other instances relatively small volumes of blood may be sufficient to have a similar effect. The amount of antibodies which pass through the placenta from the moth-

er's circulation into that of the fetus may vary widely in different cases. This fact had repeatedly been stated by pointing out the considerable differences between titers of maternal iso- and heteroagglutinins found in cord and maternal sera. The well-known variable individual ability to produce antibodies should also be mentioned.

The incidence of hemolytic disease is greater in families in which the father is homozygous Rh positive (DD) because the mother is then subected to the stimulus of fetal antigen in each successive pregnancy whereas with a heterozygous husband the stimulus is likely to be active only in some pregnancies.

The amount of antigen that enters the maternal circulation may greatly vary depending on the extent of damage to the placental barrier which is considered important for the transmission of the antigen—a controversial subject often discussed by many authors. In each of the cases presented, the placenta did not reveal anything unusual which would have attracted special attention—another finding suitable for the theory of the existence of a placental barrier and its protective mechanism.

At birth, these three infants could not be distinguished from normal unsensitized infants either on their clinical course or on hematological examinations. Evidence of sensitization could only be demonstrated by a direct positive Coombs test and the presence of some maternal antibodies in the cord serum. Because of the absence of any sign of morbidity the infants were left without any treatment. Later on, when manifestations of the hemolytic process became apparent—marked pallor, drop in red cell count and hemoglobin—the infants of the second and third mothers had to be transfused.

The degree of normality of this type of cases is quite difficult to define. Many of the recorded cases in the literature never revealed complete serological and hematological findings and the infants, in these instances, were never observed critically enough during the entire neonatal period which would have helped to determine a limit of normality. Pickles'[9] suggestion appears, therefore, appropriate, "that cases of maternal immunization with clinically normal infants should be assessed as strictly as those of true hemolytic disease in order to try and determine the relationship of this type of sensitization and the classic disease."

Yannet and Lieberman,[10] and Snyder, Schoenfield, and Offerman,[11, 12] reported several cases of severe mental deficiency, the cause of which could be attributed by them to the Rh antigen. Such defectives were regarded to be born without any obvious sign of hemolytic disease.

Drummond and Watkins[13] examined three families in which there were children who suffered from enlargement of liver and spleen, and whose condition presented various diagnostic problems. It could be shown that in two of the three families the mother had been sensitized to the Rhesus factor.

Such observations call for great caution in regard to various problems which may arise. It is evident that the occurrence of such residual effects of hemolytic disease are unpredictable unless a constant vigilance is kept over the child not only through its neonatal

period but also throughout its entire period of infancy into that of adolescence.

Summarizing the findings of the observed cases and compared with those found in the literature, the conclusion is reached that, at any time, it will be extremely difficult to speak of normal sensitized infants or normal infants of sensitized mothers, etc.

In order to point out a more specific relationship between maternal sensitization and the neonatal status of the infant, the term "latent hemolytic disease of the newborn infant" appears very suggestive, thus designating the inactive stage of the hemolytic process in the immediate neonatal period.

In spite of the various improved transfusion techniques, the proper management of hemolytic disease of the newborn infant still remains rather problematic. As shown in our case reports, periodic antenatal titer determinations together with hematological and serological findings at birth turned out to be insufficient for proper evaluation of the clinical condition of the newborn infant, and much direct bedside observation had to be made regarding an indication for possible blood transfusion.

Because of this complete lack of correlation which is sometimes noted between maternal titer, degree of anemia at birth, and the severity of the disease in the infant, Pickles[9] has stressed the importance on the estimation of the bilirubin content of the cord blood and the degree of sensitization of the child's cells, together with the red cell regeneration response, upon which the type of treatment will depend. According to her, an infant with a serum bilirubin level of 2.5 mg. per cent or less in spite of a high degree of sensitization will do well, whereas a serum bilirubin above that level together with evidence of a high degree of sensitization will call for immediate treatment.

Bilirubin determinations on the cord serum were actually performed in two of our observed cases and found below 2.5 mg. per cent; the cord serum of the third case appeared normal in color. Studies on red cell regeneration response were unfortunately not carried out.

SUMMARY

Three cases of maternal Rh sensitization are presented suggesting that, in many instances, hemolytic disease in the newborn infant is not directly correlated with the degree of maternal isoimmunization.

In the immediate neonatal period the hemolytic process may be latent and the impression of a perfectly healthy infant simulated. In the following weeks after birth, a marked anemia characteristically is in a remarkable contrast to the general well-being of the infant who invariably also shows signs of red cell sensitization by a still positive Coombs test.

Caution is stressed in regard to the various problems which may arise from eventual residual effects in such cases, as there is still great lack of knowledge as to the exact effect of the maternal antibody on the infant's vital organs. That other effects than hemolysis may eventually play an important role in the causation of mental deficiency due to Rh incompatibility appears plausible.

REFERENCES

1. Dockeray, G. C., and Sachs, H.: [illegible] Antibodies in the Maternal Circulation Without Clinical Manifestations of Erythroblastos. in the [illegible], J. Immunol. 48: 241, 1944.
2. Goldbloom, A., and [illegible]: Anti-Rh Agglutinins in [illegible] Without Symptoms of [illegible] in the Newborn Infant, [illegible] 83, 1946.
3. Kariher, D. H., and Miller, D. [illegible]: Evidence of Maternal Rh Sensitization Without Evidence of Hemolytic Disease in the Newborn, Am. J. M. Sc. 212: [illegible] 1946.
4. Carter, B. B.: Maternal Rh Sensitization and the Clinically Normal Child, Am. J. Obst. & Gynec. 54: 879, 1947.
5. Donohue, W. L., and Fremes, [illegible]: Maternal Isoimmunization Without Evidence of Clinical Erythroblastosis Fetalis in the Newborn, J. [illegible] Med. 33: 526, 1948.
6. Howard, J., Lucia, S. P., [illegible] and McIvor, B. C.: A [illegible] Cases of Normal Rh P[illegible] Born to Sensitized Rh Negative Women, [illegible]. J. Surg., Obst. & Gynec. 55: 401, 1948.
7. [illegible] M. S., Kuans, W. J., and Jahn, [illegible] in Rh Isoimmunization in Pregnancy, J. Obst. & Gynec. 54: [illegible], 1947.
8. [illegible]: The Problem of Rh Sensitization, J. Newark [illegible] Hosp. 2: 3, 1950.
9. Pickles, M. M.: Hemolytic Disease of the Newborn, Oxford, 1949, Blackwell Scientific Publications, pp. 43 [illegible].
10. [illegible], H., and [illegible], S.: The Rh Factor in the Etiology of Mental Deficiency, Am. J. Ment. Deficiency 49: 132, 1944.
11. [illegible], L. H., Schoenfeld, M. D., and [illegible], E. M.: The Rh Factor and Feebleminedness, J. Hered. 34: 3, 1943.
12. [illegible], L. H., Schoenfeld, M. D., and [illegible], E. M.: A Further Note on the Rh Factor and Feeblemindedness, J. Hered. 38: 4[illegible], 1947.
13. [illegible], A. G.: [illegible] and Neonatal Jaundice and [illegible], J. Ped. 36: 36, 1950.

MELENA IN THE NEWBORN INFANT

IRVING H. ROZENFELD, M.D., AND JAMES R. MCGRATH, M.D.*
CHICAGO, ILL.

THE quantity of blood necessary for the formation of a tarry stool in adults has been variously estimated at 50 to 100 c.c.,[1, 2] but similar data for newborn infants have not previously been reported. Some older editions of pediatric texts[3, 4] refer to bleeding from a cracked nipple as a possible cause of melena in nursing infants, which would suggest that a relatively small amount of ingested blood would produce melena. The following case made us aware of the need for this information.

CASE REPORT

J. M., Unit No. 470890. The infant was born after a full-term, uncomplicated pregnancy, and was delivered by outlet forceps following episiotomy. Respirations began spontaneously within one minute. The birth weight was 3,300 grams. The initial physical examination disclosed no abnormalities and the baby was started on breast feedings. By the fifth day, meconium had disappeared and the stools were yellow. He regained his birth weight on the sixth day of life, and was circumcised on the eighth day. There was no evidence of an abnormal bleeding tendency at this time.

On the tenth day of life, the baby passed two tarry stools. Examination showed a well-hydrated baby who was sleeping quietly and appeared normal. The skin and mucous membranes showed no pallor, jaundice, petechiae, or ecchymoses. There was no evidence of bleeding in the mouth or nasopharynx. The lungs and heart were normal, and the abdomen was soft and nontender. The liver edge was felt 2 cm. below the right costal margin, and the spleen and kidneys were not palpable. Hemoglobin was 17.2 grams per 100 ml. On the same day it was discovered that the mother's left nipple was cracked and bleeding. Breast feeding was discontinued that afternoon. During the night, there were two more tarry stools. On the following day, examination again showed a healthy looking infant in no distress and without evidence of disease. The hemoglobin was 15.0 grams per 100 ml., and the red blood count 5,300,000. The white blood count was 12,900; platelets 312,000; reticulocytes 1.2 per cent; hematocrit 45 per cent; differential, stab forms 13 per cent, segmented forms 42 per cent, lymphocytes 38 per cent, monocytes 6 per cent. The prothrombin time was 18 seconds (control 17 seconds).

A stool passed later that day was yellow in color and showed one plus positive reaction for blood on benzidine test. The following day, the twelfth day of life, another yellow stool was only questionably positive to benzidine. The hemoglobin remained at 15.0 grams. The baby was discharged with the diagnosis of "melena due to ingestion of blood (mother's milk?)."

METHOD OF STUDY

This study was undertaken to determine the amount of ingested blood necessary to cause tarry stools in the newborn infant. Fresh blood was obtained by femoral puncture from a baby, heparinized with powdered heparin and introduced into the same baby's stomach by means of a Levine tube. A record was then kept of the time, color, and consistency of each

From the Department of Pediatrics, Bobs Roberts Memorial Hospital and the Chicago Lying-in Hospital, University of Chicago.
*Present address: Bellevue, Wash.

stool for the next thirty-six hours. In all cases, the infants had yellow stools which were free of meconium for at least twenty-four hours, and none was breast fed or receiving any iron preparation.

The procedure was carried out with twenty-four infants, ranging in weight from 2,280 to 3,975 grams. The results are shown in Table I.

TABLE I

NUMBER OF BABIES TESTED	AMOUNT OF BLOOD GIVEN (C.C)	NUMBER SHOWING MELENA
8	2.0	0
1	2.6	1
7	3.0	4
8	5.0	6

TABLE II

WEIGHT (GRAMS)	C.C. OF BLOOD INGESTED	TIME OF FIRST APPEARANCE (HOURS)	NUMBER OF TARRY STOOLS
2,325	2.6	7	1
2,525	3.0	11	3
2,445	3.0	7	2
2,570	3.0	17	1
3,583	3.0	8	4
2,280	5.0	12	2
2,400	5.0	12	3
3,220	5.0	9	1
2,760	5.0	7	1
3,320	5.0	12	1
3,365	5.0	8	2

DISCUSSION

Of the eight who were given 2 c.c. of blood, none had a tarry stool. One baby received 2.6 c.c. of blood and passed one tarry stool. Four of the seven given 3 c.c. of blood produced tarry stools, as did six of the eight given 5 c.c. of blood. Data on those infants who showed melena are given in Table II.

These results indicate that as little as 2.6 c.c. of blood, when ingested, may cause a tarry stool in the newborn infant. Had a larger number of infants been tested, it is possible that a smaller amount of blood may have been found to be occasionally sufficient.

It has also been shown that as long an interval as seventeen hours may elapse between the ingestion of blood and the passage of a tarry stool.

CONCLUSIONS

1. A study has been undertaken to determine the amount of ingested blood that is necessary to produce tarry stools in the newborn infant.

2. Melena may be produced by as little as 2.6 c.c. of ingested blood, and was produced in four of seven babies given 3 c.c. and in six of eight babies given 5 c.c. of blood.

3. Of the group tested, those infants who passed tarry stools did so from seven to seventeen hours after the blood was placed in the stomach.

REFERENCES

1. Daniel, W. A., and Egan, B. S.: J. A. M. A. **113**: 2232, 1939.
2. Schiff, L., Stevens, R. J., Shapiro, N., and Goodman, S.: Am. J. M. Sc. **203**: 409, 1942.
3. Thursfeld and Paterson: Diseases of Children, Baltimore, 1928, Wm. Wood and Co., p. 90.
4. Abt, I.: Pediatrics, Philadelphia, 1924, W. B. Saunders Co., vol. IV.

RESULTS OF ADMINISTRATION OF VITAMIN B_{12} TO NEWBORN INFANTS

ROBERT F. CHINNOCK, M.D., AND HARVEY W. ROSENBERG, M.D.
LOS ANGELES, CALIF.

FOR some time it has been known that certain factors are effective in producing a more rapid growth response in experimental animals. Vitamin B_{12} has been found to be one of the various factors which has been effective.[1] The report by Wetzel and associates[2] that vitamin B_{12} was effective when given by mouth in producing a more rapid growth response has stimulated interest as to its possible use in promoting more rapid weight gain in young infants and also in prematurely born infants. Chow[3] reports greater weight gain in malnourished children and to a lesser extent in well children receiving vitamin B_{12} orally than when the vitamin was not given.

However, other studies have failed to corroborate these findings. Downing[4] did not find a significant increase in weight when vitamin B_{12} was given to prematurely born infants. Rascoff and associates[5] also report a lack of increase in weight.

Several in presenting data on the use of vitamin B_{12} supplementation refer to the growth of infants, but weight gain is the only phase of growth discussed.

A study was begun in September, 1950, to determine if the oral administration of vitamin B_{12} in the first two months of life would promote more rapid weight gain, and, if greater weight gain were noted early, to see if it would continue after the vitamin was discontinued. The growth rate was also evaluated during the period of vitamin administration.

MATERIAL AND METHODS

Full-term infants were placed in three groups. Infants in Group I were given vitamin B_{12} for the first sixty days of life, those in Group II were given vitamin B_{12} for the first thirty days, and in Group III (controls) no vitamin B_{12} was given. The vitamin B_{12}* (crystalline vitamin B_{12} in aqueous solution 15 μg per cubic centimeter) was given in a calibrated dropper which supplied 5 μg of the vitamin. The infants were given 5 μg of B_{12} daily during the period of the vitamin administration.

A placebo of water with vegetable coloring was given to the control group and to Group II after the vitamin was discontinued. All infants received formulas of evaporated milk, water, and Karo syrup, and were on a modified self-regulating schedule. Orange juice and vitamins A and D were also given. The vitamin or placebo was started with the first feeding after birth and added to the milk in one bottle daily.

On leaving the hospital parents were instructed to return with the infant every two weeks for observation of general nutritional status and measurements. From 0 to four observa-

From the Department of Pediatrics, College of Medical Evangelists.

Aided by a grant from the Squibb Institute for Medical Research.

*Supplied by E. R. Squibb and Sons, New York, N. Y.

tions were made on each child during the eight-week interval. Results were used only from infants who made at least two return visits.

Ninety infants were begun in the study but for various reasons, such as failure to report for observation, failure to give the vitamin as directed, illness, etc., all could not be included in the final results. Included in the data reported are twelve infants in Group I (B_{12} entire peroid), eleven in Group II (B_{12} first thirty days), and six in Group III (control).

of Group II 3,330 grams (7 pounds 5 ounces), and of Group III 3,335 grams (7 pounds 5 ounces). The mean birth lengths were: Group I 50.07 cm. (19.9 in.), Group II 50.08 cm. (19.9 in.), and Group III 49.6 cm. (19.5 in.).

RESULTS

As seen in Fig. 2 the gains of the twelve infants receiving B_{12} the entire period were lower than the gains of the control group. However, a statistical analysis using a "t" test based on estimating sigma from the range[7]

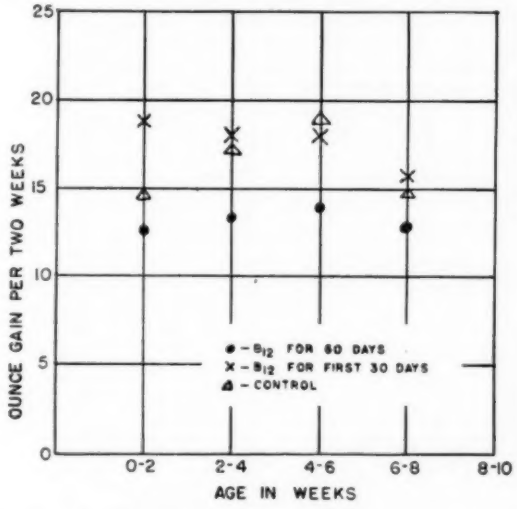


Fig. 1.—Weight gains per two-week interval of infants receiving vitamin B_{12} for the first sixty days of life, for the first thirty days of life, and of a control group.

Weight and growth curves were visually fitted to the observed data. Weight and height readings were taken from the curves at 2, 4, 6, and 8 weeks of age. Average weight gains per two-week interval, and average weight above birth weight were computed with results illustrated in Figs. 1 and 2.

The mean birth weight of Group I was 3,490 grams (7 pounds 11 ounces),

shows that such a difference in means would occur in more than 5 per cent of such studies of babies whose gains were as variable as ours. Hence we conclude the difference is not significant, that is, this study does not lead us to believe that vitamin B_{12} fed infants gain weight less rapidly than infants not fed vitamin B_{12}. There is no reason from this study to suspect

that infants fed B_{12} gain more rapidly than the control babies.

A similar result arises on analyzing our length data (Fig. 3).

From Figs. 2 and 3, it is seen that giving vitamin B_{12} for one month, then withholding it, made no significant difference.

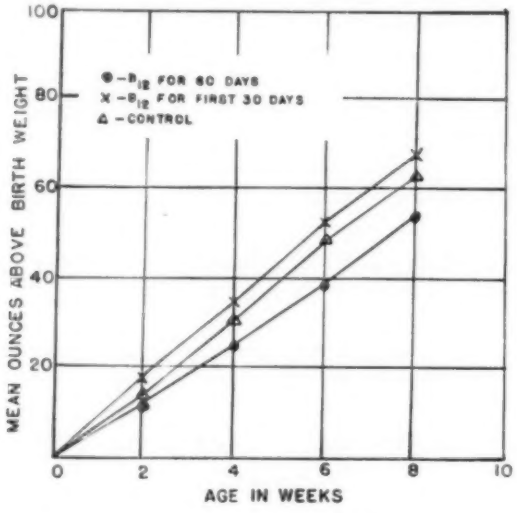


Fig. 2.—Mean weight gain above birth weight of infants given vitamin B_{12} for the first sixty days of life compared to those receiving B_{12} for the first thirty days and to a control group.

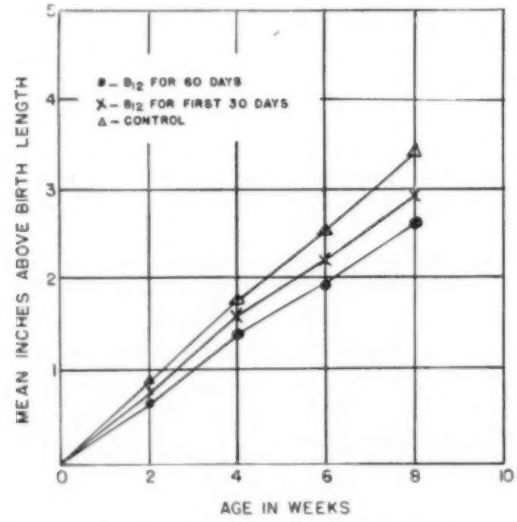


Fig. 3.—Mean increase in length during the first sixty days of life of infants receiving vitamin B_{12} for the entire period, for the first thirty days, and of a control group

DISCUSSION

The failure of increase of weight noted by us is at variance to other reports.[2, 3] There is apparently no widespread deficiency of vitamin B_{12} among the infant and child population as evidenced by the relative rare case of megaloblastic anemia. The infant artificially fed on a standard cow's milk formula receives at least as much vitamin B_{12} as the infant who is breast fed inasmuch as cow's milk has more B_{12} than human milk.[6]

One would expect that if supplemental vitamin B_{12} were to produce greater weight gain in the normal infant, that those receiving formulas of whole cow's milk or equal parts of evaporated cow's milk and water would gain weight more rapidly than the breast-fed infant, but such has not been noted.

It is interesting to note that other studies[4, 5] also show that the infants given supplemental vitamin B_{12} showed weight gain to be at a slightly lower rate than the control group. However, these results, when taken together with ours, are not great enough to be conclusive.

SUMMARY

1. The weight and height progress of twelve infants receiving 5 μg of vitamin B_{12} daily for the first eight weeks of life is compared to eleven infants receiving it for the first four weeks of life and to a control group.

2. No greater weight gain or increase in length was noted in the group receiving the vitamin B_{12}.

The assistance of Paul Johnson, Ph.D., in the statistical evaluation is gratefully acknowledged.

The cooperation of the staff members of the White Memorial Pediatric Clinic has been of great aid in making this study possible.

REFERENCES

1. Luecke, R. W., McMillen, M. N., Thorp, F., Jr., and Boniece, Joanna R.: The Effect of Vitamin B_{12} Concentrate on the Growth of Weanling Pigs Fed Corn-Soybean Diets, Science **110**: 139, 1949.
2. Wetzel, N. C., Fargo, W. C., Smith, I. H., and Helikson, J.: Growth Failure in School Children as Associated With Vitamin B_{12} Deficiency—Response to Oral Therapy, Science **110**: 651, 1949.
3. Chow, B. F.: Sequelae to the Administration of Vitamin B_{12} to Humans, J. Nutrition **43**: 323, 1951.
4. Downing, D. F.: Failure of Vitamin B_{12} to Promote Growth of Premature Infants, Science **112**: 181, 1950.
5. Rascoff, H., Dunewitz, A., and Norton, R.: The Weight Progress of Premature Infants Given Supplementary Feedings of Vitamin B_{12}, J. PEDIAT. **39**: 61, 1951.
6. Castle, W. B., Elvehjem, C. A., May, C. D., Welch, A. D., Zuelzer, W. W., and Butler, A. M.: Report to A. M. A. Council on Foods and Nutrition—Vitamin B_{12} and Folic Acid in Infant Nutrition, J. A. M. A. **146**: 1028, 1951.
7. Hoel: Introduction to Mathematical Statistics, New York, 1947, John Wiley & Sons, Inc., p. 165.

A CASE OF CONGENITAL CYSTINURIA

HARMEN PRAKKEN, M.D.
HENGELO, HOLLAND

A BOY, 3 years, 1 month of age, was admitted to the clinic for ischuria paradoxa. It was an acute sequela to difficult micturition which had occurred occasionally during the previous twelve months. During this period the parents had noted that the urine was often turbid.

On examination, the fundus of the bladder was high above the symphysis and urine was dripping from the meatus. Just above the root of the penis a hard, ring-shaped thickening was noted, and solid obstruction to catheterization occurred at this level.

About fifteen stones were removed from the urethra under ethyl chloride anesthesia, the largest of which was pea-sized. The stones were brittle and were found to consist of cystine and calcium oxalate. The urine contained many crystals of cystine and many leukocytes.

The father of the boy was of a nervous type and suffered from nocturnal enuresis. The paternal grandfather had died of a renal affection. The urine of all available members of the family was examined and was negative for cystine both microscopically and by the sodium cyanide-sodium nitroprusside test, up to the third generation on the maternal side. The father's urine gave a positive Brand reaction but no cystine crystals were found in the fresh specimen.

The patient was thin, weighing 13 kilograms, and of normal height for age. Intelligence seemed normal for age. A concomitant convergent strabismus was present and a marked genu valgum (Fig. 1).

CLINICAL OBSERVATION AND DIFFERENTIAL DIAGNOSIS

Escherichia coli was found in the urinary culture which was sensitive in vitro to sulfadiazine and streptomycin, but courses of treatment with these drugs did not clear up the pyuria.

Stones in the bladder were demonstrated roentgenologically (Fig. 2) and were confirmed cystoscopically. The renal pelvis seemed free of stones. The right ureter was only partially filled on the intravenous pyelogram. No rickets or other anomalies were found in skeletal x-ray films.

Blood serum examination showed the following: total nitrogen 12.17 per mille, nonprotein nitrogen 0.27 per mille, serum albumin 5.49 per cent, serum globulin 1.95 per cent, albumin-globulin quotient 2.8.

Serum phosphate was within normal range, 4.70 mg. per cent.

The absence of nephrotic dwarf growth with glycosuria and hypophosphatemia, the clinical and roentgenological absence of rickets or other bone anomalies, and the fact that no changes were demonstrated in the corneas or conjunctivae due to cystine crystals were thought sufficient ground to exclude definitely cystinosis (Lignac's disease) or Toni-Fanconi's disease.

Evidently this was a case of hereditary cystinuria, in which stone forma-

Fig. 1.

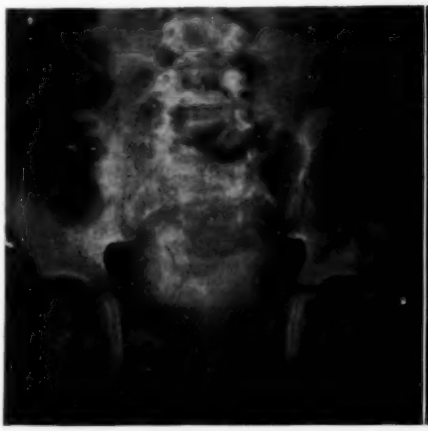


Fig. 2.

Fig. 3.

Fig. 2.—Stone shadows in the bladder region.
Fig. 3.—No stones are visible after one year, four months.

tion in the urinary tract occurred as early as in the beginning of the second year of life. This is considered to be very rare. So far as we could ascertain, the renal function did not seem to be disturbed as there was good excretion of the roentgen contrast medium and good reabsorption of glucose and phosphate. The fact that the nonprotein nitrogen content was normal supported this impression. This determination, however, could give no information regarding the free amino acid metabolism, such as of cystine, because only a small part of the total nonprotein nitrogen is supplied by these substances.

DETERMINATION OF THE AMINO ACIDS AND DISCUSSION OF THE RESULTS

J. H. P. Jonxis and S. K. Wadman (Zuiderziekenhuis, Rotterdam) were kind enough to carry out this examination. Their findings were as follows:

Chromatography of the urine; much cystine and lysine, little asparaginic acid, glycine, serine, alanine, and glutaminic acid. Chromatography of the serum: fair amounts of cystine, further serine, glycine, glutaminic acid, and alanine, but no lysine. Titration of the α-amino nitrogen content (according to Albanese): urine 0.153 mg. per milliliter, serum 0.082 mg. per milliliter. Titration of the cystine content (according to Sullivan and Hese): urine 10 mg. per cent (8 per cent of the total α-amino nitrogen content), serum 3.2 mg. per cent (4.5 per cent of the total α-amino nitrogen content). The urine chromatogram of a little sister born meanwhile showed a marked lysine ring. The remainder of the amino acids were not visible or only hardly so. No cystine could be titrated in her urine.

Incontinence made it impossible to determine the daily amount of urine, even with an indwelling catheter. Thus the absolute amount of α-amino nitrogen excreted in the urine could not be calculated. For this reason it was impossible to repeat the experiments of Brand and associates,[1] confirmed by Lewis and collaborators,[2] which showed that administration of cystine in the food has no influence on the cystinuria, but that extra methionine or cysteine increases the excretion of cystine.

Although the determinations were carried out carefully, the results must be judged with some reserve, on account of the poor specificity of the amino acid determinations in blood and urine. Moreover, the serum concentrations change quickly, apparently under the influence of nutrition and tissue metabolism.

It may be deduced that the serum cystine concentration is moderately increased. Brown and Lewis[3] give somewhat lower values as normal (0.7 to 1.1 mg. per cent).

It is also clear that in this case the cystinuria was not a symptom of general amino aciduria, as the α-amino nitrogen concentration of the urine was low and there were only sparse and weak rings on the chromatogram of the urine.

Attention should further be paid to the associated lysinuria with absence of serum lysine and a fairly high glycine concentration in the serum with low glycinuria. This partly agrees with the observations of Yeh and co-workers,[4] who, applying microbiological methods in a case of cystinuria, found an increase in the excretion of cystine, arginine, and lysine

in the urine and a decrease in the excretion of glycine and histidine. Lysinuria in cystinuria was also observed by Ackermann and Kutscher[5] and Hoppe-Seyler.[6]

A remarkable point also is that a considerable amount of glycine could be demonstrated in the serum, while the excretion was small. In most cases glycine, histidine, and cystine seem to be predominant among the free amino acids.[7, 8]

PATHOGENESIS

Since it is known that cystine occurs normally in small quantities in the urine, the clinical picture of cystinuria is considered to be an increased excretion of cystine in the urine. Here it is difficult to draw the dividing line between normal and pathological on the statistical data available. Formation of cystine stones, however, is sufficient reason to regard the cystinuria as a pathological phenomenon.

Freudenberg[9] considers cystinuria and cystinosis (cystine accumulation disease, to which belong Lignac's disease and cases of Toni-Fanconi's disease) as diseases with the same pathogenesis: a congenital partial disturbance in the amino acid metabolism. The difference in syndrome is considered to be dependent on the age of the child. Since up to now only cystinosis and no cystinuria had been observed in very young children, Freudenberg was led to believe that in these cases the kidneys were not yet mature enough to excrete cystine. Children with cystinosis usually die early; therefore, this clinical picture is not seen at more advanced ages, in contrast to cystinuria. This would be the reason why at a later age accumulation of cystine in the body, and thus Lignac's disease, does not arise.

If we agree with Freudenberg that in this case a disturbance in the metabolism is primary, then cystinuria should be the result of an extraordinarily early maturation of a kidney function. This seems strange, however.

It is simpler to consider this pathological phenomenon as a congenital partial disturbance of the renal function and not as a particular renal effort. This also agrees better with the investigations of Beyer and associates,[10] Kirk,[11] Russo and collaborators,[12] Ferguson and co-workers,[13] and Wright and associates.[14] From these it appears that in dogs the free amino acid concentration of glomerulus filtrate and plasma is the same. As the loss in the urine is only slight, they should be almost completely reabsorbed by the tubules. This is the case in dogs without threshold value (arginine and lysine excepted). Even with a raised cystine level in the blood the concentration in the urine need not therefore be increased. When in man the amino acids follow the same course, cystinuria cannot be explained from a congenital disturbance of the metabolism, but by an elective deficiency of the tubular reabsorption. This view is acceptable in this case, as the early age at which the phenomenon occurred in our patient does not support the "kidney maturation theory" as an auxiliary hypothesis to that of disturbed metabolism.

It must be left undecided whether and cystine metabolism, for it remains there is an anomaly in the methionine a problem that in spite of the cys-

tinuria the blood cystine is moderately increased or certainly not decreased. The lysinuria in this child, however, seems to be a mere disturbance of an elective kidney function, because no lysine could be demonstrated in the chromatogram of the serum. Further, McCune and associates[15] and Dent[16] arrive at the conclusion that in cystinosis certain amino acids are excreted, because of incomplete reabsorption in the tubules.

TREATMENT

Initially, the urine was kept alkaline, by which crystal formation in the urine was prevented. The protein content in the diet was fixed at 2 Gm. per kilogram of body weight; for the rest the child had a mixed diet. Choline was given by mouth for the following reason: It appears that the cystine in the urine originates mainly from the methionine in the food.[1, 2] The first stage of this catabolism may be the demethylation of methionine to homocysteine.[17] The methyl groups which are freed by this process can be used for the synthesis of choline and creatinine,[18] but this reaction is reversible; thus there exists a continuous interchange of methyl groups between choline and methionine. Du Vigneaud coined the name "transmethylation" for this phenomenon. But evidently homocysteine can replace methionine as an amino acid for growth only when the diet contains sufficient methyl groups with choline or betaine.[19, 20, 21]

Later, sodium benzoate was given in addition to choline, with the purpose of dissolving the stones by a higher hippuric acid concentration of the urine. Groen[22] obtained success by this method in a case of cystinuria in an adult. The following prescription was ordered:

Sodium benzoate	0.500 Gm.
Potassium citrate	0.350 Gm.
Sodium citrate	0.500 Gm.
Saccharum vanilla	0.150 Gm.
Saccharum lactis	0.250 Gm.

This was given in six doses in powder form, which the child took readily.

During clinical observation the colipyuria disappeared under this treatment, whereas sulfadiazine and streptomycin had been of no avail. The treatment with choline and sodium benzoate was continued uninterruptedly after discharge, under supervision in the polyclinic.

The child developed normally. Pyuria and cystine-crystalluria were no longer observed, but the cystine in the urine was always increased, according to the reaction of Brand, and the chromatogram of the urine also showed the same picture continuously. The stone shadows on x-ray of the bladder became less marked, and had completely disappeared one year, four months after commencing the sodium benzoate treatment (Fig. 3).

The chromatogram of the urine of the baby sister also changed little after the neonatal period.

SUMMARY

A case is described of congenital cystinuria with associated lysinuria and cystine and oxalate calculosis in a 3-year-old boy. Disturbances of micturition caused by bladder stones started as early as the age of 2 years. The observations point to a disturbance in the tubular reabsorption of cystine and lysine.

Choline was administered to the child on the supposition that this sub-

stance can supply the methyl groups for the conversion of homocysteine into methionine; the opposite of one of the reactions in the catabolism of methionine to cystine. Sodium benzoate was given by mouth, with the aim of dissolving stones by a higher hippuric acid concentration in the urine. The accompanying colipyuria soon disappeared. On continued treatment no stones were visible radiologically after one year, four months. Cystinuria without crystal formation in the fresh urine was found in the father, and a little sister showed lysinuria in the neonatal period and later, without cystinuria and without or with only slight excretion of the other free amino acids.

REFERENCES

1. Brand, E., Cahill, G. F., and Harris, M. M.: Proc. Soc. Exper. Biol. & Med. **31**: 348, 1933.
2. Lewis, H. B., Brown, B. H., and White, F. R.: J. Biol. Chem. **114**: 171, 1936.
3. Brown, B. H., and Lewis, H. B.: J. Biol. Chem. **138**: 705, 1941.
4. Yeh, H. L., Frankl, W., Dunn, M. S., Parker, P., Hughes, B., and György, P.: Am. J. M. Sc. **214**: 507, 1947.
5. Ackermann, D., and Kutscher, F.: Ztschr. f. Biol. **37**: 355, 1912.
6. Hoppe-Seyler, F. H.: Ztschr. f. physiol. Chem. **214**: 267, 1933.
7. Dunn, M. S., Camien, M. N., Shankman, S., and Block, H.: Arch. Biochem. **13**: 207, 1947.
8. Sheffner, A. L., Kirsner, J. B., and Palmer, W. L.: J. Biol. Chem. **175**: 107, 1948.
9. Freudenberg, E.: Advances in Pediatrics, 1949, vol. IV, pp. 265-292.
10. Beyer, K. H., Wright, L. D., Russo, H. F., and Patch, E. A.: Am. J. Physiol. **146**: 330, 1946.
11. Kirk, E.: Acta med. Scandinav. **89**: 450, 1936.
12. Russo, H. F., Wright, L. D., Skeggs, H. R., Tillson, E. K., and Beyer, K. H.: Proc. Soc. Exper. Biol. & Med. **65**: 215, 1947.
13. Ferguson, F. P., Eaton, A. G., and Ashman, J. S.: Proc. Soc. Exper. Biol. & Med. **66**: 582, 1947.
14. Wright, L. D., Russo, H. F., Skeggs, H. R., Patch, E. A., and Beyer, K. H.: Am. J. Physiol. **149**: 130, 1947.
15. McCune, D. J., Mason, H. H., and Clarke, H. T.: Am. J. Dis. Child. **65**: 81, 1943.
16. Dent, C. E.: Biochem. J. **41**: 240, 1947.
17. Butz, L. W., and Du Vigneaud, V.: J. Biol. Chem. **99**: 135, 1933.
18. Simmonds, S., and Du Vigneaud, V.: J. Biol. Chem. **146**: 685, 1942.
19. Rose, W. C., and Rice, E. E.: J. Biol. Chem. **130**: 305, 1939.
20. Du Vigneaud, V., Chandler, J. P., Moyer, A. W., and Keppel, D. M.: J. Biol. Chem. **131**: 57, 1939.
21. Simmonds, S., Cohn, M., Chandler, J. P., and Du Vigneaud, V.: J. Biol. Chem. **149**: 519, 1943.
22. Groen, J.: Nederl. tijdschr. v. geneesk. **94**: 570, 1950.

TWELVE CASES OF TESTICULAR TUMORS OCCURRING DURING INFANCY AND CHILDHOOD

CARL RUSCHE, M.D.
HOLLYWOOD, CALIF.

TUMORS occurring in the early periods of life, and particularly those developing in infancy and the first three decades, exhibit many peculiarities not found in neoplasms at later age periods. Malignancy is one of the leading causes of death in childhood; however, testicular tumors occur infrequently. The incidence of malignant tumors in children classified according to site is: (1) central nervous system; (2) lymphoid tissue; (3) bones; (4) kidneys; (5) liver; (6) skin; (7) testes; (8) intestines; (9) tongue; and (10) ovary.

The cellular structure of the testicular tumors confirms the belief that these growths arise from totipotent sex cells which are capable of producing tissue representing any derivative of the three primary germinal layers. The tumors are similar to those found in adults, not only as to structure but also in their clinical course and response to treatment.

Childhood testicular tumors are not as uncommon as the earlier treatises on the subject would lead us to believe. However, the occurrence of these neoplasms in infants and children may be considered relatively infrequent when compared to the same lesions in adults. Julien[1] reviewed the literature in 1925 and collected 137 cases. Kretschmer[2] quoted Gilbert's[3] summation of the literature from 1803 to 1942 of 5,500 cases of malignant testis, of which 131 occurred in children under 15 years of age. Teratomas[4, 5, 6] comprise the majority of neoplasms affecting the external genitalia before puberty. In Dean's[7] series of 500 testicular tumors, eight occurred in children between 1 and 14 years. Embryonal carcinoma[2, 8, 9, 10, 11, 12] has been reported with increasing frequency. Seminoma, the most common adult testicular tumor, is exceedingly rare, with two cases recorded, one by Hardowin and Potel,[13] and the other by Fitzgerald.[14] I[15] had one such case in a 13-year-old pseudohermaphrodite. Ewing[16] submitted a case of a primary lymphosarcoma in the testis of a 5½-year-old child; and Williams[17] reported an incident of a testicular sarcoma in a child who was alive three years after extirpation. Chorionic epithelioma[18] of testis has been found in infants. I was unable to find any incident of a teratocarcinoma occurring during childhood.

Bengin testicular growths occur with less frequency, with the most common pathologic entity being interstitial cell tumors.[19, 20, 21] Stevens[22] reported the occurrence of a dermoid cyst in a 16-month-old child; and Rosenthal[23] submitted a case of hemangioma in an infant.

The data which comprises this study of twelve histopathologically diagnosed testicular tumors were complied from the disease indices for the past twenty-five years of the Childrens Hospital, and Hollywood Presbyterian Hospital,

From the Department of Surgery (Urology), University of Southern California Medical School, and the Childrens Hospital.

Los Angeles. Of the twelve tumors, eight were adult teratomas, three embryonal carcinomas, and one dermoid cyst (Table I).

CLINICAL FINDINGS

A distinguishable characteristic of tumors in an immature testis is their development during the early years of a child's existence. Of this group of twelve cases, 75 per cent of the lesions occurred prior to the third year of life. Testicular neoplasm was present at birth in four instances, with a histopathological diagnosis of adult teratoma in two cases, dermoid cyst in one, and embryonal carcinoma in the other case. Julien[1] reported this finding in twenty of the cases in his study.

In children, as in adults, there are no discernible pathognomonic symptoms of a testicular tumor. Painless enlargement of one testicle is the usual presenting symptom and was present in ten of the cases. Testicular pain was associated with the two cases with widespread dissemination of the disease at time of diagnosis. The interval between the onset of testicular enlargement and surgical removal of the tumor varied from one month to four years. The slow growing lesion which was present for four years was a dermoid cyst. Expediency rather than procrastination should be employed to determine the type of tumor present.

A malignant neoplasm must be considered in the differential diagnosis of any intrascrotal enlargement occurring before puberty. When palpation reveals a symmetrically enlarged testis, of varying size, usually firm, round, which does not transilluminate, the presumptive diagnosis should always be malignancy. The presence of an abdominal mass when the testis is not present in the scrotum should suggest the possibility of testicular malignancy, although cryptorchidism was not a predisposing factor in this group, nor has it been a salient feature in other studies of testicular tumors in childhood. The only acceptable diagnostic procedure is an immediate orchiectomy with serial microscopic sections of the surgical specimen to determine the nature of the tumor. There was no instance of radical orchiectomy among this group. Postoperative roentgen-ray therapy is dependent upon degree of differentiation of neoplasm. Because these tumors run such a rapidly fatal course, it is essential that the proper diagnosis be

TABLE I. TWELVE CASES OF TESTICULAR TUMORS CLASSIFIED AS TO AGE, PATHOLOGIC ENTITY, AND STATUS

AGE AT TIME OF DIAGNOSIS	SIDE OF TUMOR	TYPE OF TUMOR	ROENTGEN-RAY THERAPY	INTERVAL AND STATUS SINCE DIAGNOSIS
4 yr.	R	Dermoid cyst	No	Alive, 9 yr.
6 mo.	R	Embryonal carcinoma	No	Alive, 5 yr.
17 mo.	L	Embryonal carcinoma	No	*Dead*, 3 mo.
2½ yr.	L	Embryonal carcinoma	Yes	*Dead*, 4 mo.
1 mo.	R	Adult teratoma	Yes	Alive, 8 yr.
11 mo.	R	Adult teratoma	No	Alive, 13 yr.
15 mo.	R	Adult teratoma	No	Alive, 2 yr.
16 mo.	R	Adult teratoma	No	Alive, 8 yr.
2 yr.	L	Adult teratoma	No	Alive, 8 yr.
2½ yr.	L	Adult teratoma	No	Alive, 4 yr.
6 yr.	L	Adult teratoma	No	Alive, 24 yr.
12 yr.	L	Adult teratoma	No	Alive, 8 yr.

made without delay and effective treatment be given promptly.

DERMOID CYST

Dermoid cysts are a rare pathologic entity which develop slowly and are usually observed before the testicle is fully matured, though they have been known to make their initial appearance in adult life.[24] The histogenesis of these lesions is unknown. A testicular dermoid is separated from the testicular tissue by a capsule, and is found within the confines of the tunica albuginea or attached to the testicle. The growth contains a variation of stratified squamous epithelium, hair follicles, sebaceous glands, and sweat glands. Anderson[25] states: "Among the tissue components of dermoids, those of the skull are most frequent and frequency of the various tissue components decrease corresponding to the lower location and distance from the head." The growth is considered to be benign in nature, as there is no recorded instance of dissemination or malignancy developing in a true testicular dermoid cyst.

Progressive testicular enlargement had been present since birth in the child who had a dermoid cyst removed at the age of 4 years. There was a round, hard, nonfluctuant mass involving the right testis. When the gross specimen was sectioned there was present a cystic structure containing thick mucoid material, yellowish cheesy material, and hair. In the center of the dermoid tubercle there was a white mass of tissue containing hair. The testicle itself was completely destroyed.

Microscopic sections revealed a small amount of compressed glandular testicular structure, and one area showed the presence of cells consistent with

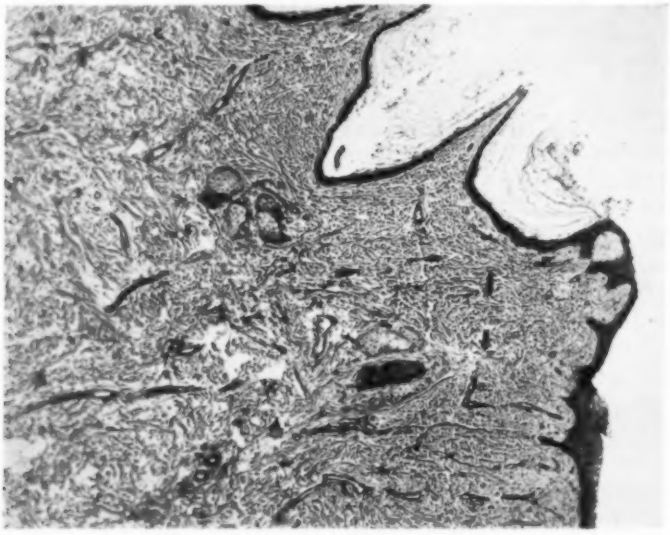


Fig. 1.—Photomicrograph of testicular dermoid cyst showing the squamous epithelium and sebaceous glands. The squamous epithelium is forming papillary projections and hyperkeratosis. (×75.)

the epididymis. The dermoid cyst was covered by epithelium which varied from ciliated columnar to a squamous type of epithelium, the latter containing sweat glands and hair follicles. The base consisted of fibrous connective tissue and adipose tissue (Fig. 1).

EMBRYONAL CARCINOMA

Embryonal carcinomas are commonly characterized by a high degree of malignancy and a very unfavorable prognosis. However, one of the three children with this type of tumor is alive and well five years following a simple orchiectomy. Removal of the malignant testis was not performed until the infant was 6 months of age, as the testicular enlargement which was present at birth was presumed to be only a hydrocele. Histopathological examination disclosed the presence of the embryonal carcinoma associated with the hydrocele. No demonstrable metastases have been found on periodic examinations, and the child is developing normally.

The metastases of malignant testicular tumors occur by way of the lymphatics or blood stream. The most common site of lymphatic involvement is the retroperitoneal nodes, including those around the kidney pedicle which give rise to symptoms consistent with primary renal tumor. There was one such incident in this group. A child had complained of abdominal pain of three weeks' duration which was accompanied by episodes of vomiting and anorexia. The only urinary symptom observed by the mother was frequency of two months' duration. The physical examination disclosed a pale, chronically ill white child, 2½ years of age. Abdominal palpation revealed a firm, fixed, slightly tender mass filling the entire left side of the abdomen. The scrotal contents were considered normal. Retrograde pyelograms disclosed the left kidney pelvis to be displaced outward and downward. The upper calyx was not well outlined, suggestive of a filling defect consistent with neoplasm.

The clinical and roentgenographic findings were in accordance with those present in Wilms' tumor. Preoperative roentgen therapy was administered, and the mass diminished rapidly in size which is the usual response of a radiosensitive renal tumor. A few days prior to the nephrectomy a small mass was palpable in the left scrotum. The testicle was enlarged, hard, slightly nodular, with involvement of the epididymis; all these changes had taken place within the six-week period preparatory to nephrectomy.

The surgical specimen consisted of the left kidney and hilar mass measuring 8 cm. in length, 3½ cm. in width, and 3½ cm. in thickness. There was a thickened capsule which measured approximately 5 mm. in thickness that had been stripped from the surface of the kidney leaving a smooth, light, pale kidney surface, scattered over which were small reddish areas. The kidney capsule was composed of a dense, reddish purple, boggy material in which some fat was seen. On medial longitudinal section through the kidney, a very pale renal architecture was seen, and the cortex measured 5 mm. in diameter. The minor calyces and pelvis did not appear remarkable with the exception of an occasional small red area in the mucosa of the pelvis.

Microsections through the capsule of the kidney disclosed the presence of

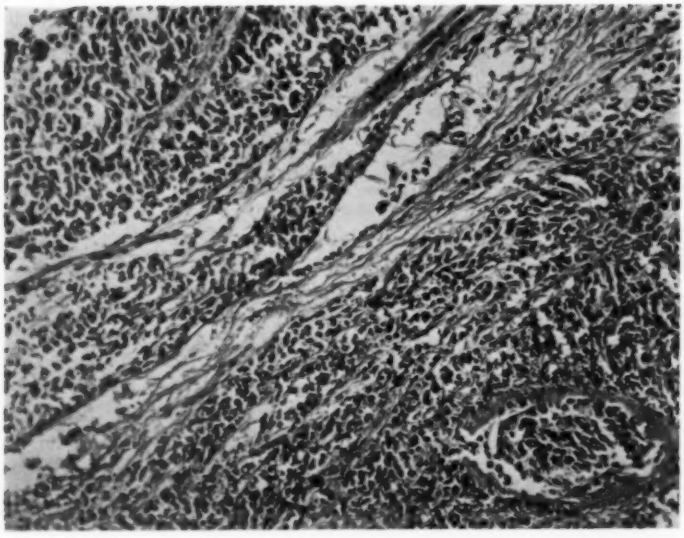


Fig. 2.—Photomicrograph of metastatic embryonal carcinoma to kidney. Embryonal cells in the renal tissue. (×150.)

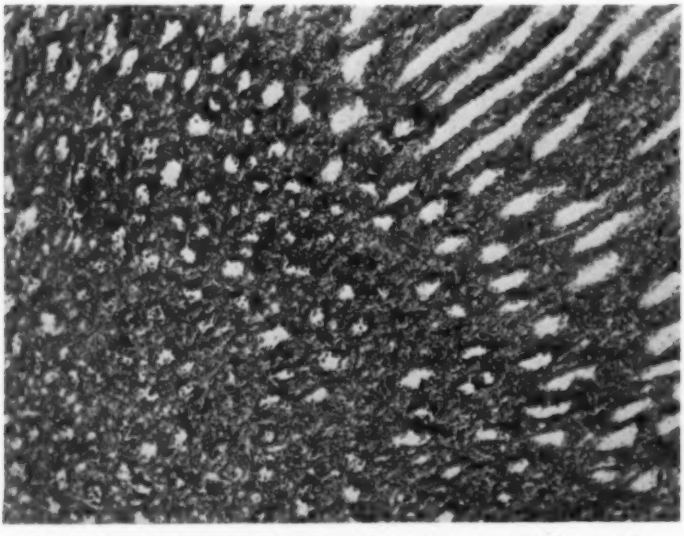


Fig. 3.—Photomicrograph of embryonal carcinoma of testicle. (×75.)

pink-staining fibrous connective tissue containing many spindle-shaped cells. The capsule was greatly widened. Scattered throughout the section, there were many large mononuclear cells containing a dark brown pigment. Large areas of hemorrhage were also seen. There were occasional clumps of smooth muscle fibers and groups of adult fat cells, and patches of lymphoid tissue. Also occasional masses of large mononuclear cells with abundant granular cytoplasm were present. The section through the kidney showed many proximal convoluted tubules as well as collecting tubules containing casts of pinkish blue lamellated material. The lining cells of the convoluted tubules were swollen and somewhat granular. Sections from the hilar region showed peripheral infiltration with spindle-shaped cells. *Histologic diagnosis:* Metastatic embryonal carcinoma (Fig. 2).

The probability of a primary testicular lesion was suggested and an orchiectomy carried out. The gross specimen was comprised of an oval, pearly gray, smooth, encapsulated mass measuring 3.5 × 1.5 × 1.5 cm., which invaded the epididymis. Microsections of the left testis confirmed the presence of a primary embryonal carcinoma (Fig. 3). Death occurred four months after the nephrectomy was performed.

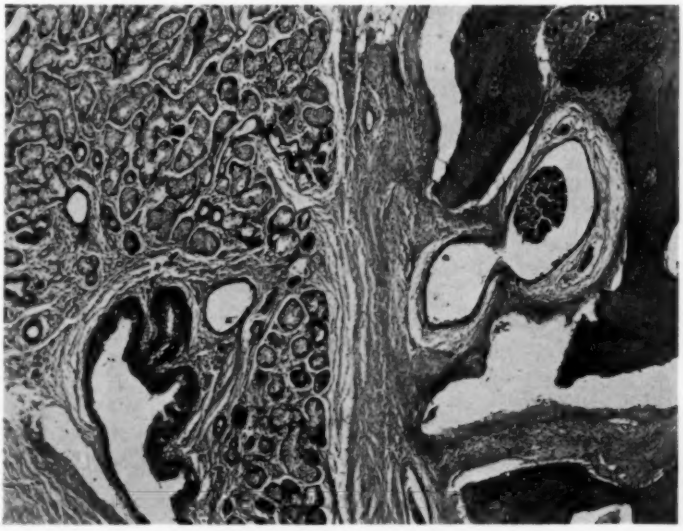


Fig. 4.—Photomicrograph of testicular teratoma showing bone and bronchial epithelium. (×75.)

The child, 17 months of age, had enlargement of the testis for six months prior to orchiectomy, at which time there was retroperitoneal involvement. Death occurred three months after surgical removal of embryonal carcinoma.

ADULT TERATOMA

Adult teratomas formerly were classified as benign or malignant. Friedman[26] states: "Benign teratomas

should be called adult teratomas because they only have adult tissue. They aren't benign so far as the patient is concerned." These tumors are radioresistant and simple orchiectomy is the recommended procedure.

The mean age for the development of teratoid testicular tumors in adults is between 25 and 27 years. Six of these childhood tumors occurred before the third year of life, the other two developed at the ages of 6 and 12 years, respectively.

Testicular enlargement at birth was observed in two instances among these eight cases of adult teratomas. In one case, the presumptive diagnosis was hydrocele; however, bloody fluid was obtained on aspiration and a right orchiectomy performed when the infant was 1 month of age. Roentgen-ray therapy totaling 2,350 r was administered postoperatively, and the child is alive and well eight years later. The adult teratoma in the other instance which was present at birth was removed when the child was 16 months old.

The patient who has lived twenty-four years subsequent to orchiectomy is the father of two children. Testicular enlargement was present at 4 years of age, though the testis was not removed until two years later. Microscopic sections showed areas of myxomatous tissue, true bone, and bone marrow (Fig. 4).

The prognosis of adult teratomas in this study is excellent. Six of the children may be considered cured, four have lived eight years, one thirteen years, and another twenty-four years. The two children who are alive two and four years since orchiectomy show no evidence of dissemination of the disease at this time. Adult teratomas in older age groups are not characterized by such a favorable survival period.

COMMENTS

Twelve cases of childhood testicular tumors, eleven malignant and one benign, are presented together with a survival analysis, and the methods employed in treatment are reviewed. Four of these tumors were present at birth.

There are few diseases which cause enlargement of scrotal contents in childhood, therefore every intrascrotal swelling occurring before puberty should be considered a malignant tumor until proved otherwise.

Malignant tumors of the testicle are a local disease for a certain period of time. If the diagnosis is made and simple orchiectomy performed during this period the hope of cure is excellent. Therefore, after a diagnosis of tumor is established, immediate extirpation is mandatory. However, when extensive metastases are present, orchiectomy is seldom performed.

Preoperative irradiation in tumors of the testicle should be condemned for the following reasons: (1) valuable time may be lost before the tumor is removed; (2) irradiation destroys the original architecture of the tumor, complicating an accurate microscopic diagnosis; (3) benign tumors inadvertently are irradiated; (4) the spermatogenic function of the remaining testis may be destroyed. Postoperative irradiation is dependent upon the histologic properties of the tumor. Teratomas which account for the largest percentage of testicular neoplasms in children are radioresistant. Seminomas which occur extremely in-

frequently in childhood are the most radiosensitive tumor.

Cryptorchidism as a predisposing cause of malignancy has been disputed since 1851 when LeComte first asserted that undescended organs frequently became malignant. However, in this series of cases there was no instance of tumor development in an ectopic organ.

The favorable survivance experienced by this group of cases is noteworthy; ten of these twelve patients are alive without evidence of disease, eight of whom have lived five years or longer and may be considered cured; six of which were adult teratomas, one an embryonal carcinoma, and one a dermoid cyst. Testicular tumors are usually characterized by a high grade of malignancy and rapid growth in adults as well as in children.

REFERENCES

1. Julien, R. R.: Études des tumeurs du testicle chez l'enfant, Paris, Thesis, 1925.
2. Kretschmer, H. L.: Embryoma of the Testicle in a Five-Year-Old Child, Am. J. Surg. **76**: 99, 1948.
3. Gilbert, J. B.: Quoted by Kretschmer.
4. Dargeon, H. W.: Cancer in Children From Birth to 14 Years of Age, J. A. M. A. **136**: 459, 1948.
5. Twinem, F. P.: Benign Teratoma of the Testicle in a 3 Year Old Boy; a Case Report, J. Urol. **47**: 577, 1942.
6. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, Arch. Path. **30**: 535, 1940.
7. Dean, A. L.: Cancer in Childhood, edited by H. W. Dargeon, St. Louis, 1940, The C. V. Mosby Co., p. 44.
8. Rosenblum, A., and Robbins, M. A.: Embryonal Adenocarcinoma of the Testicle in a Three-Year-Old Child. Report of a Case, J. PEDIAT. **33**: 627, 1948.
9. Matassarian, F. W.: Embryonal Adenocarcinoma of Testicle in Infant; Case Report, J. Urol. **52**: 575, 1944.
10. Meltzer, A., and Bloom, B.: Malignant Testicular Neoplasms in Infancy; Report of a Case With Six-Year Survival, New England J. Med. **237**: 513, 1947.
11. Shane, J. H.: Tumor of the Testis in an Infant, J. Urol. **42**: 236, 1939.
12. Magner, D., and Bryant, A. J. S.: Adenocarcinoma of the Testis Occurring in Infants; Report of Two cases, Arch. Path. **51**: 82, 1951.
13. Hardowin, P., and Potel, G.: Deux observations de tumeur du testicule chez l'enfant, Bull. et. mem. Soc. Anat. de Paris **79**: 150, 1914.
14. Fitzgerald, W. L.: Quoted by Campbell, M.: Clinical Pediatric Urology, Philadelphia and London, 1951, W. B. Saunders Co., p. 730.
15. Rusche, C.: In Publication.
16. Ewing, J.: Quoted by Campbell, M.: Pediatric Urology, vol. 2, New York, 1937, The Macmillian Co., p. 308.
17. Williams, I. G.: Cancer in Childhood, Brit. J. Radiol. **19**: 182, 1946.
18. Campbell, M.: Clinical Pediatric Urology, Philadelphia and London, 1951, W. B. Saunders Co., p. 730.
19. Nation, E. F., Edmondson, H. A., and Hammack, R. W.: Interstitial Cell Tumors of the Testis; Report of Three New Cases, Arch. Surg. **48**: 415, 1944.
20. Melicow, M. M., Robinson, J. N., Ivers, W., and Rainsford, L. K.: Intersitial Cell Tumors of Testis. Review of Literature and Report of Case, J. Urol. **62**: 672, 1949.
21. Huffman, L. F.: Interstitial Cell Tumor of the Testicle; Report of a Case, J. Urol. **45**: 692, 1944.
22. Stevens, W. E.: Benign Teratomas (Dermoid Cysts) of the Testicle; a Case Report, J. Urol. **44**: 864, 1940.
23. Rosenthal, A. A.: Hemangioma of the Testis in an Infant, J. Urol. **55**: 542, 1946.
24. Dockerty, M. B., and Priestley, J. T.: Dermoid Cysts of the Testes, J. Urol. **48**: 392, 1942.
25. Anderson, W. A. D.: Pathology, St. Louis, 1948, The C. V. Mosby Co., p. 1124.
26. Friedman, N.: Proceeds of the Third Annual Urological Post Graduate Convention, 1949, p. 136.

CARDIAC COMPLICATIONS OF PERTUSSIS

MAJOR STUART H. WALKER, MEDICAL CORPS, UNITED STATES ARMY

IN RECENT years significant cardiac disease has rarely been reported to arise during the course of pertussis. However, several interesting mechanisms exist by which myocardial insufficiency might be produced in this disease. Therefore, it seemed desirable to study and report the following cases of children seen at the Contagious Division, Cleveland City Hospital, during the spring of 1950 who, without previously evident cardiac disease, developed signs of myocardial insufficiency during severe pertussis.

Ledbetter and White[1] reviewed the literature prior to 1925 concerning the effects of pertussis upon the heart. Before this date many clinicians had commented upon the cardiac strain supposedly consequent to the severe paroxysmal coughing of pertussis. Pfaundler and Schlossman[2] reported congestion of the pulmonary circulation with secondary dilatation and hypertrophy of the right ventricle, supposedly subsequent to the forced paroxysmal expiration. Herman and Bell[3] noted that 7 per cent of 300 cases of pertussis showed some cardiac dysfunction. However, despite the apparent frequency with which cardiac abnormality had previously been noted, Ledbetter and White[1] were unable to find a single instance of cardiac damage or dysfunction which could be attributed to pertussis in a review of 232 cases. They quoted personal communications from a large number of notable physicians who were agreed that pertussis had had no effect upon the heart in their experience.

Since 1925 most clinicians have apparently accepted Ledbetter and White's conclusion that pertussis does not affect the heart. No report concerning cardiac disease during pertussis could be found in the American literature since this date. Chajes-Rosenbund[4] in Germany reported that roentgenographic evidence of increase in cardiac size could be frequently correlated with severe pertussis. Thompson[5] in England reported the case of a 4-year-old girl who developed congestive cardiac failure, dramatically relieved by diuretics, during the course of pertussis. He felt that the combination of overwork during paroxysms and an acute carditis might account for the syndrome. Franconi and Frischknecht[6] in Finland have reported the frequency with which excessive tachycardia appears in severe pertussis. However, in a recent review of 137 cases of pertussis seen in New York, Rizzo[7] detected no evidence of cardiac abnormality. Nowhere in the literature has a thorough evaluation been made of the possible pathogenetic factors which might produce myocardial insufficiency during pertussis.

MATERIAL AND METHODS

During the period Jan. 1, 1950, to July 1, 1950, 159 cases of pertussis, the majority of which were mild, were

Wm. Beaumont Army Hospital, Fort Bliss, Texas.

admitted to the Contagious Division, Cleveland City Hospital, Cleveland, Ohio. Of these, three or 1.9 per cent developed findings suggestive of cardiac involvement during the course of pertussis. Persistent and excessive tachycardia, moderate enlargement of the liver, poor quality of the heart sounds, and dyspnea and orthopnea out of proportion to the severity of the pulmonary disease suggested myocardial insufficiency in each. These three cases are reported in an attempt to prove that myocardial insufficiency did occur during the course of pertussis, that it accounted for the symptomatology presented, and that it had a common pathogenesis. These three were proved cases of pertussis who, during the course of the disease, developed manifestations of a wide range of myocardial insufficiency. One patient died in cardiac failure, one developed manifest failure which continued for several weeks but subsequently disappeared, and one developed minimal signs of myocardial insufficiency without frank failure. An analysis of these three cases is undertaken to explain the mechanisms by which pertussis may produce myocardial insufficiency.

All venous pressure determinations were made using a saline manometer with the patient supine, a 20-gauge needle inserted downstream in the external jugular vein. No significant venous spasm was noted, but readings were rechecked for constancy. The neck was supported in a relaxed state, so that measurements were obtained 20 mm. above the phlebostatic axis passing through the right posterior auricular wall. During the latter part of the hospital course, it was necessary to use oral Seconal sedation to obtain adequate relaxation for a resting determination.

The significance of the venous pressure determinations was verified by comparison with determinations made in the same manner on ten other children with moderate to severe pertussis but without signs of myocardial insufficiency aged 8 months to 4 years. The resting venous pressure in the jugular vein in each of these children was between 30 and 60 mm. of saline and no elevation of venous pressure was ever elicited by abdominal compression. Hussey and Jeghers[8] and Winsor and Burch[9] have emphasized the significance of the venous pressure elevation produced by compression over the liver. These workers feel that this alteration is one of the most accurate indications of incipient cardiac failure. The venous pressure elevation at the height of the edema and cardiac enlargement in J.T. and the venous pressure rise induced by abdominal compression in E.T., thus seem decisively indicative of myocardial insufficiency and cannot be attributed to uncomplicated pertussis.

The typical paroxysmal cough, the character and duration of the disorder, and the pathognomonic white blood cell count leave no doubt that these children had pertussis. The occurrence of myocardial insufficiency with and without manifest cardiac failure seems equally definite. The enlarged heart, the liver and lung engorgement, the edema, and the venous pressure alteration could not have been produced by an other mechanism. However, no evidence of any pre-existing cardiac disease prior to the onset of pertussis was detected in any of these children.

CASE REPORTS

CASE 1.—G. C., a 4-month-old, white male infant, was admitted to the Contagious Division, Cleveland City Hospital, on March 23, 1950, because of a paroxysmal cough of seven days' duration and the development of varicella on March 17.

Physical examination at this time revealed a well-hydrated infant in no respiratory distress with a typical moderate varicella eruption in various stages of healing. The temperature was 36.9° C., the heart rate was 120 per minute, the respiratory rate was 24 per minute, and the weight was 5,900 grams. The heart sounds were of fair quality. No cardiac enlargement was detected. The lungs showed scattered coarse râles and rhonchi. The liver was palpable 3 cm. below the costal margin. A moderate paroxysmal cough typical of pertussis was noted. White blood count was 32.6 thousand per cubic millimeter with 87 per cent lymphocytes.

Except for a moderate weight loss to 5,600 grams by March 30 and the continuance of occasional moderately severe paroxysms, the child did well until April 2. On April 3 the temperature rose to 39.0° C. However, except for an increased respiratory rate and tachycardia of 160 per minute, no other significant changes were noted. On April 4 the temperature was still 39.0° C., the respiratory rate was 50 per minute, the heart rate averaged 180 and was frequently above 200 per minute. At this time, though the lungs showed no râles, there was marked emphysema and dyspnea. The child was lethargic and occasional twitching of the hands was noted. Oxygen and steam administration were commenced.

On April 5 the findings were accentuated. The temperature was 40.0° C., the respiratory rate varied between 70 and 100 per minute, the heart rate was estimated as high as 250 per minute, and the first heart sound became muffled and distant. The chest was markedly emphysematous and moist râles appeared at both bases. Roentgenogram of the chest revealed emphysema, patchy atelectasis, a large area of atelectasis involving the right upper lobe, slight cardiac enlargement, and a small, right-sided pneumothorax. Dyspnea and restlessness were extreme and the child became slightly cyanotic despite oxygen administration. The liver progressively enlarged to a level of 6 cm. below the costal margin. The chest was tympanitic to percussion in most areas particularly beneath the sternum. Eyeball pressure caused gradual slowing of the cardiac rate to approximately 220 per minute. Electrocardiogram revealed a sinus tachycardia with normal P-R and Q-T intervals. The T-waves were upright in Leads I and II, and diphasic in Lead III. Lumbar puncture revealed 18 crenated red blood cells with a protein concentration of 80 mg. per 100 c.c. Digitalization was attempted with 0.2 mg. of Cedilanid intravenously.

On April 6 moderate improvement was noted. The liver edge was only 3 cm. below the costal margin. Dyspnea was lessened, but the marked emphysema persisted. On April 7 the heart was enlarged to percussion for the first time, and the liver was palpable and tender 4½ cm. below the costal margin. Dyspnea and restlessness increased. The child was extremely lethargic, refused to suck, seemed very weak, and had several loose stools. His weight had risen to 6,100 grams despite the very poor oral intake, and periorbital and genital edema was noted.

On April 8, with extreme dyspnea and tachypnea, the child again became cyanotic, and the heart rate again rose to approximately 250 per minute. The edema had become more marked. Generalized twitching continued despite phenobarbital. During the afternoon of this day, the extremities became cold, the skin mottled, and the heart sounds very weak. Six hours later respiration ceased and, despite cardiac and respiratory stimulants, the child died.

Autopsy revealed marked emphysema, focal atelectasis, and interstitial pneumonia throughout all lung areas. Bronchiolitis with exudate, obstruction, and peribronchiolitis was apparent. It was felt that pulmonary interstitial emphysema was present, but specific techniques to demonstrate its occurrence were not carried out. No abnormalities of the endocardium, the valves, or of the great or coronary vessels were detected. The myocardium appeared normal without evidence of inflammation or abnormal glycogen deposition in the sections which were obtained. The liver was enlarged and showed passive congestion. The brain appeared normal.

CASE 2.—J. T., Negro male, aged 3½ years, was admitted to the Contagious Division, Cleveland City Hospital on May 3, 1950, because of a nonproductive cough of 2½ weeks' duration, fever, anorexia, and lethargy.

Physical examination at the time of admission revealed an acutely ill, lethargic child complaining of abdominal pain with a temperature of 38.5° C., heart rate of 145 per minute, respiratory rate of 60 per minute, and blood pressure of 85/60 mm. Hg. Though the chest was hyperexpanded, the lungs seemed entirely normal; despite the tachypnea no râles or evidence of consolidation or obstruction were detected. No cardiac abnormalities were noted; the heart was not enlarged, the sounds were of good quality, and there were no murmurs. The liver was enlarged and palpated 3 cm. below the costal margin. The abdomen was distended and diffusely tender. Severe paroxysmal coughing, typical of pertussis, was noted. Laboratory examination revealed white blood count 65,000 per cubic millimeter of which 80 per cent were lymphocytes.

On May 5, fine and coarse râles throughout both lung fields, marked emphysema, dyspnea, and moderate cyanosis were detected. The child was placed in oxygen and steam, and Chloromycetin therapy, 0.5 Gm. daily, commenced. On May 8 marked dyspnea was apparent, the liver was tender and pulsating 6 cm. below the costal margin, the lung fields were filled with fine and coarse râles, and cyanosis was present despite oxygen administration. The child was extremely weak and irritable. The heart rate was 180 per minute, the heart sounds were of poor quality, and a presystolic gallop rhythm was present. Roentgenograms of the chest revealed emphysema, slight cardiac enlargement with a cardiothoracic ratio of 0.50, and bilaterally increased hilar markings. The child was digitalized with intravenous Cedilanid, 0.03 mg. per kilogram. For the next ten days, he received 0.032 Gm. of digitalis leaf orally, two days out of every three.

On May 9 he seemed moderately improved, dyspnea was less, cyanosis had disappeared, and râles were markedly diminished though still present. The liver had receded but was still tender, 4½ cm. below the costal margin. Severe paroxysmal coughing, lethargy, and orthopnea continued. The resting venous pressure in the external jugular vein was 180 mm. of saline.

On May 15, the child seemed definitely worse. The liver was 7 cm. below the costal margin and was exquisitely tender. More fine râles were noted and the heart sounds were again of very poor quality with a presystolic gallop rhythm. For the first time periorbital edema was noted.

On May 16 generalized edema was apparent and body weight had increased from 34.5 pounds on admission to 40.5 pounds. Dyspnea was again marked. Dullness and diminished breath sounds were apparent at the right base posteriorly. Chest roentgenograms revealed generalized cardiac enlargement and straightening of the left border with a cardiothoracic ratio of 0.57, increased hilar markings, a large emphysematous bleb above the left diaphragm, and a small pleural effusion at the right base. The resting venous pressure in the external jugular vein was 260 mm. of saline. Mercuzanthin, 0.5 c.c. daily, was commenced.

By the following day, May 17, a marked diuresis had occurred, the

weight was down to 36 pounds, and only minimal edema remained. The liver had receded to 3 cm. below the costal margin and was no longer tender. Only a few scattered râles remained in the lung fields, though the signs of pleural effusion and slight dyspnea continued. The heart rate was still 150, the sounds were of poor quality, and the gallop rhythm persisted. The venous pressure had decreased to 160 mm. of saline.

temperature normal, and the weight 32 pounds. On May 25 a roentgenogram of the chest revealed only emphysema, increased hilar markings, a slightly enlarged heart with a cardiothoracic ratio of 0.51, and further enlargement of the pulmonary conus. Diuretics were discontinued. The heart rate, temperature, and respiratory rate remained normal and the weight continued at approximately 33.5 pounds for the remainder of the

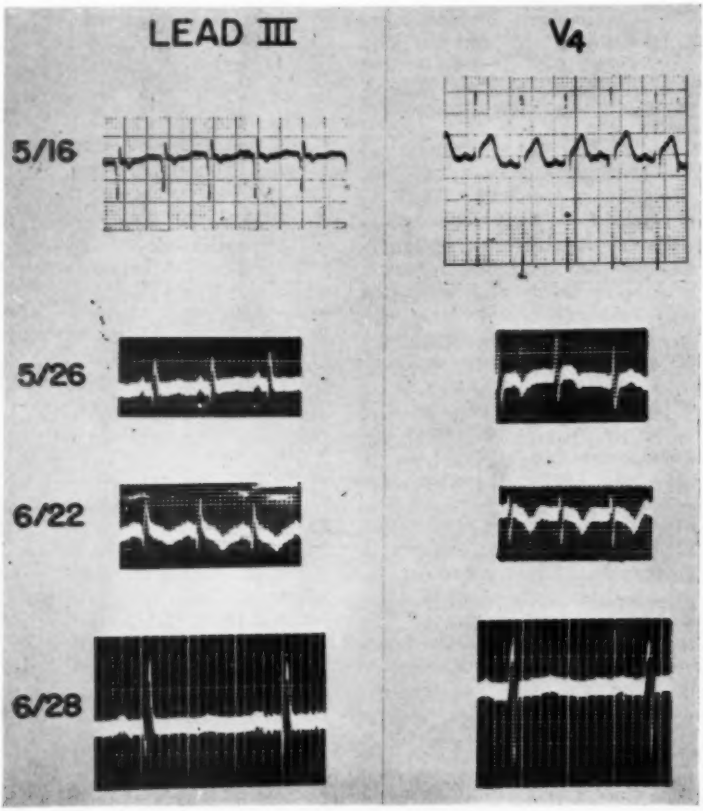


Fig. 1 (Case 2).—Serial electrocardiograms showing progressive T-wave changes.

By May 20, though moderate abdominal pain continued with the liver 4½ cm. below the costal margin, the edema had disappeared completely, the resting venous pressure was 60 mm. of saline, the heart rate was 120, the

hospital stay. The venous pressure remained normal at about 40 mm. of saline, but continued to show a rise of between 70 and 130 mm. of saline with compression over the liver until June 12. The liver gradually diminished in

size and was only barely palpable on June 20. Paroxysms gradually decreased in severity and were rarely heard after June 7. Though the lung fields had been essentially clear to auscultation since May 27, the child continued to sleep in the sitting position without support until June 7.

There was no evidence of renal disease at any time. Urine examinations were always entirely normal. On May 16, blood urea nitrogen was 19.6 mg. per 100 c.c., and total protein was 7.2 Gm. per 100 c.c. with an albumin-globulin ratio of 1.58. No cardiac murmurs were detected and blood cultures revealed no growth. No pathogenic organisms were grown from nose or throat cultures. Blood carbon dioxide determinations were within

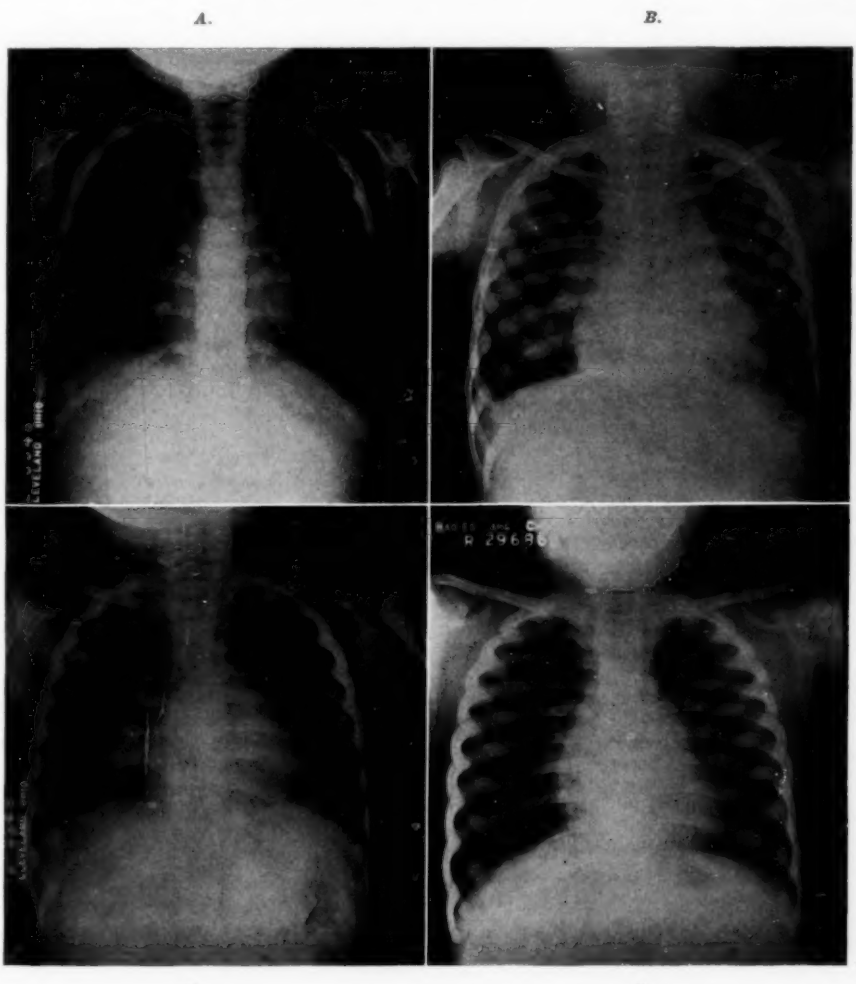


Fig. 2 (Case 2).—Serial roentgenograms showing cardiac dilatation and hypertrophy and enlargement of the pulmonary conus. *A*, May 8, 1950; *B*, May 16, 1950; *C*, June 5, 1950; *D*, Oct. 17, 1950.

normal limits. The erythrocyte sedimentation rate was within normal limits throughout the course of myocardial inefficiency. Skin tests with tuberculin and histoplasmin were negative.

The child was discharged from the hospital on June 22, but was readmitted on July 3 because of the recurrence of manifest cardiac failure with rapidly increasing dyspnea, orthopnea, cyanosis, and cough. Physical examination revealed fine râles throughout both lung fields, accentuated pulmonic second sound, enlarged tender liver 4 cm. below the costal margin, and marked hyperexpansion of the chest. Gradual clearing of all signs and symptoms referable to myocardial inefficiency occurred in conjunction with digitalis and mercurial diuretics. With an average respiratory rate of 28 per minute, the CO_2 combining power was found to be 90 volumes per cent with a plasma chloride level of 74.2 meq. per liter and a plasma sodium level of 135 meq. per liter apparently indicating respiratory acidosis secondary to the marked pulmonary alveolar and bronchiolar damage. The CO_2 combining power gradually decreased to 68 volumes per cent by July 13. Marked abdominal distention and diffuse tenderness were found to be associated with ascites at this time. Roentgenograms of the chest again revealed diffuse cardiac enlargement chiefly of the right ventricle, straightening of the left cardiac border, and emphysema.

Gradual clearing of all signs and symptoms referable to myocardial insufficiency followed, and by August 1 the chest was free of râles, the abdomen was no longer distended, and the liver was just palpable at the costal margin. When last examined in September, there was no symptomatology referable to the heart or lungs though the chest remained hyperexpanded and roentgenograms revealed persistent cardiac enlargement and emphysema.

Electrocardiograms taken throughout the course of this illness revealed certain distinctive abnormalities. Regular sinus rhythm with slight right axis deviation in an almost vertical heart was apparent in all records. The P-R and QRS intervals were always within normal limits. Average measurements for K using the formula $K = \frac{QT}{\sqrt{RR}}$ were never higher than 0.41. The progressive inversion and subsequent return to the original upright position of the T waves in standard Lead III and in the right unipolar precordial leads were the most distinctive abnormalities noted. The greatest T-wave changes in the precordial leads occurred in Lead V_4 (which always showed a typical right ventricular R-S pattern). At the height of clinical failure on May 16 the T waves were upright in these leads, but became progressively inverted until June 22 when almost complete cessation of clinical myocardial inefficiency was apparent. Return to the upright position progressed steadily thereafter without retrogression during the recurrence of manifest failure in early July (see Fig. 1).

CASE 3.—E. T., an 18-month-old Negro female, was admitted to the Contagious Division, Cleveland City Hospital on June 7, 1950, because of severe paroxysmal cough of seven days' duration.

Physical examination at the time of admission revealed a well-nourished child in moderate respiratory distress with a temperature of 38° C., a heart rate of 120 per minute, a respiratory rate of 60 per minute, a blood pressure of 80/55 mm. Hg, and a body weight of 22 pounds. A moderately severe paroxysmal cough typical of pertussis was noted. The chest was hyperexpanded and hyperresonant with scattered coarse and fine râles throughout both lung fields. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The liver was not palpable. Laboratory examination revealed a white blood count of 136,000 per cubic millimeter with 78 per cent lymphocytes. Pertussis hyperimmune rabbit serum,

60,000 units total, was administered over a period of three days. Procaine penicillin, 300,000 units daily, and Chloromycetin, 1.0 Gm. daily, were commenced.

Because of increasing emphysema, dyspnea, and exudate within the lungs, oxygen and steam were administered continuously from June 7 to June 15. A generalized convulsion followed the prolonged apnea associated with one severe paroxysm. The child appeared to be extremely dyspneic and orthopneic but the heart sounds were of good quality and the liver was not palpable. On June 14 the venous pressure in the external jugular vein was 35 mm. of saline, the temperature had become normal, the heart rate was 120 per minute, and the respiratory rate was 30 per minute.

On June 17 the heart sounds were of poor quality and the liver was palpated 3 cm. below the costal margin. Roentgenogram of the chest at this time revealed emphysema, increased hilar markings, and a cardiothoracic ratio of 0.50. The configuration of the heart was normal. The first heart sound at the apex continued to be muffled and a soft systolic murmur was apparent on June 20. The pulmonic second sound was noted to be accentuated at this time. On this day and on June 21, though the resting venous pressure continued at 35 mm. of saline, a rise of 130 mm. was produced by compression over the liver.

On June 23, the heart rate was 120 per minute, the respiratory rate was 40 per minute, and a presystolic gallop rhythm was noted at the apex. This latter finding became increasingly prominent until June 26 when it was marked. At this time the emphysema seemed more marked, the liver was still 3 cm. below the costal margin and seemed very tender. Coarse râles were still apparent throughout both lung fields. No abnormal response to liver compression was elicited after June 21. During the week ending June 26, the child gained 2 pounds despite relatively poor food and fluid intake and occasional emesis which accompanied the continued moderately severe paroxysmal coughing.

Observation until July 6 revealed gradual subsidence of signs and symptomatology relevant to the heart. The quality of the heart sounds improved, the heart rate diminished to between 90 and 100 per minute, and the liver receded to a level 1 cm. below the costal margin. Repeated electrocardiographic recordings revealed no significant abnormalities. The child was essentially asymptomatic at the time of discharge on July 6 and emphysema was the only detectable physical abnormality.

PATHOGENESIS

Pre-existing Cardiac Disease.—There is no evidence that any pre-existing cardiac disease was present in any of these cases. The lack of any typical murmurs and the return of the heart toward normal preinsufficiency size and configuration after the recession of failure in J. T. mitigate against the presence of any congenital cardiac abnormality. The enlargement of the pulmonary conus noted in the later roentgenograms of J. T. was not present in the first films and seemed to have developed during rather than prior to the pertussis. These findings and the lack of any suggestive history of rheumatic fever in these very young children seem to contraindicate any pre-existing rheumatic heart disease. No respiratory disease was noted in these histories which could have produced chronic cor pulmonale. Hypertension was not detected. At autopsy there was no evidence of pre-existing cardiac disease in G. C. Thus, it seems probable that in these cases myocardial insufficiency was consequent to some factor which appeared during the course of pertussis. If pre-existing cardiac disease was present, some additive event occurred during pertussis

which precipitated the clinical syndromes observed.

Myocarditis.—Inflammation of the myocardium has been found at autopsy by Saphir and Amromin[10] in 38 per cent of a large series of patients with pneumonia. No clinically manifest cardiac failure was noted prior to death in these cases. Thomson and associates[11] did not confirm these findings in a small series of autopsied patients who died with pneumococcus pneumonia. However, these workers did demonstrate, during pneumonia, the development of a characteristic transient electrocardiographic pattern consisting of T-wave depression and inversion in Leads I, II, and V_4 which may or may not have indicated transient myocardial injury. However, it seems probable that a diffuse myocardial injury, which microscopically appears to be a spotty interstitial myocarditis may occur with pneumonia and may possibly have occurred in our cases, each of whom undoubtedly had a pneumonic process in addition to other pulmonary changes. The electrocardiographic pattern found in our cases, J. T. and E. T., was not that noted by Thomson and associates but could possibly have been occasioned on a similar basis.

A myocarditis that could be attributed to *H. pertussis* has never been reported. However, pathological evidence of myocarditis has been found in a vast array of infectious diseases, including nonspecific upper respiratory infections (Saphir and Gore[12]). Thus, it is not improbable that *H. pertussis* or some secondary viral or bacterial invader commonly associated with pertussis may produce a toxic myocarditis.

No evidence of myocarditis was apparent in any sections taken from the myocardium at autopsy in G. C. However, as Saphir has pointed out, myocarditis may readily be missed if numerous sections are not made. The electrocardiographic pattern of myocarditis is extremely variable. No changes may occur, or as Friedberg[13] states variable T-wave changes similar to those found in our cases may be seen. Prolongation of the Q-T interval is frequently found in myocarditis. Taran and Szilagyi[14] have demonstrated the frequency with which this change appears in rheumatic myocarditis. The Q-T interval, as evaluated by the formula $K = \frac{QT}{\sqrt{RR}}$, was within normal limits in each of our cases. Thus, although none of the findings in these cases is inconsistent with a myocarditis, whether consequent to pneumonia, secondary invading organisms, or to *H. pertussis*, this diagnosis cannot be verified.

Ventricular Stress.—The clinical manifestations of myocardial dysfunction were consistent with right ventricular insufficiency alone. The venous pressure elevation and hepatic enlargement could have been consequent to isolated right ventricular disease. The pulmonary manifestations could have been the signs of local disease or evidence of expansion of the extracellular fluid compartment consequent to right ventricular failure. Thus, right ventricular stress might account for the entire clinical pattern.

Consequent to interference with the venous return to the right ventricle during forced expiration, an unusually large inflow may occur during the excessive inspiration which follows the paroxysms of pertussis. This will increase the work of and dilate the right ventricle as the older writers pointed

out (Musser[15] and Pfaundler and Schlossman[2]). However, the degree of increase in venous return occasioned by the excessive inspiratory effort of the pertussis paroxysm does not seem comparable to the tremendous increases in venous return which Yeomans and collaborators[16] and Beck and Holman[17] found were necessary to produce extension beyond the critical fiber length and manifest failure in the normal heart. We have not noted any definite correlation between the severity of paroxysmal coughing and the development of myocardial insufficiency. Certainly extremely severe paroxysmal coughing has been noted in many children who have not developed myocardial insufficiency. Some other or at least some additional factor must operate to occasion myocardial dysfunction in the few cases in which it appears.

An increase in the peripheral resistance in the pulmonary circuit may arise subsequent to the increased intra-alveolar tension, anoxia, and pulmonary interstitial emphysema of severe obstructive pertussis as will be clarified later. Such an increase in peripheral resistance could conceivably cause a sufficient increase in right intraventricular residual blood to extend the fibers beyond their critical length. Only pulmonary embolism has been reported to produce such a syndrome, and this commonly results in early death. Fineburg and Wiggers[18] have demonstrated experimentally that pulmonary resistance can be increased by applying a clamp to the pulmonary artery in dogs without any evidence of right ventricular failure until a certain critical level is reached. Beyond this level rapid elevation of venous pressure with equally rapid fall in cardiac output resulted in manifest cardiac failure and early death. The tremendous increase in peripheral resistance (58 per cent decrease in vascular cross section) required to occasion this syndrome and the rapid course of failure thereafter does not seem consistent with the clinical course observed in these cases.

However, a pattern of right ventricular insufficiency consequent to pulmonary hypertension has been described in pulmonary embolism, emphysema, and other chronic pulmonary disease states which is apparently distinct from the suddenly apparent, rapid, right ventricular failure demonstrated experimentally by Wiggers. This clinical combination of marked pulmonary disease and slowly progressive right ventricular insufficiency seems quite similar to the cases reported herein. Wood[19] demonstrated that a consistent electrocardiographic pattern of T-wave inversion in Lead III and the right precordial leads accompanied this right ventricular stress, whether due to the moderate prolonged overwork associated with chronic emphysema or due to the sudden extreme overwork associated with pulmonary embolism. He found that the same electrocardiographic pattern might accompany myocarditis (rheumatic or diphtheritic) or pneumonia. As this pattern may be produced by the known myocardial injury associated with myocarditis, it is reasonable to assume that it indicates myocardial injury when found in association with right ventricular overwork. These electrocardiographic changes are proportional to the degree of ventricular stress and in the acute instances are frequently associated with clinical failure (Wood). Conversely, Wood states that he has

seen no reasonably proved case of pulmonary embolism with right ventricular insufficiency that failed to show this electrocardiographic pattern. The electrocardiographic patterns in the reported cases seem to indicate that a predominantly right ventricular injury was present. The T-wave inversion in Lead III and the T-wave changes in the right precordial leads in J. T. are consistent with right ventricular stress.

The progressive and persistent enlargement of the pulmonary conus, and the accentuated pulmonic second sound noted in J. T. and E. T. are highly suggestive of pulmonary hypertension. Anoxia has been demonstrated to increase the peripheral resistance in the pulmonary circuit (Friedberg[13]). The persistent mild anoxia consequent to bronchiolar obstruction and the recurrent severe anoxia associated with paroxysmal coughing may have increased pulmonary peripheral resistance in these cases. The alveolar ectasia of the compensatory and obstructive emphysema noted in each may have produced a sufficient decrease in the functioning peripheral pulmonary bed to create a significant increase in pulmonary peripheral resistance. Though these factors are of undoubted importance, a possibly more significant factor was the probable presence of pulmonary interstitial emphysema.

Macklin and Macklin[20] have demonstrated that pulmonary interstitial emphysema is a frequent complication of many pulmonary diseases and may cause great interference with pulmonary blood flow. Their work demonstrated that any factor which increases the pressure gradient between the alveolus and the pulmonary vessel sheaths may permit rupture of air into these sheaths with subsequent vascular compression. In pertussis all three factors which may induce this alveolar rupture combine to an unusual degree: (1) focal atelectasis with compensatory local alveolar ectasia secondary to the diffuse bronchiolar disease, (2) diminished pulmonary blood flow secondary to the obstructed venous return during the paroxysmal expiration, and (3) increased intrapulmonic pressure associated with the forced expiration.

Macklin and Macklin point out that the infrequency with which this condition is diagnosed does not mitigate against its presence. They emphasize that occult interstitial emphysema is the more malignant because it may be under greater than atmospheric pressure until it has free egress to the mediastinum and subcutaneous tissues where it may be clinically recognized. These workers emphasize that once alveolar rupture has occurred, further intense inspiratory efforts increase alveolar distention and the accumulation of perivascular air. As this accumulated air interferes with pulmonary elasticity, it stimulates increased dyspneic inspiratory efforts and a cyclic increase in interstitial emphysema results. Then "airlock" appears as the chest is maintained in a hyperexpanded position with rapid shallow inspiratory excursions. With this progressive accumulation of air in the vascular sheaths, distinct vascular compression, increase in pulmonary peripheral resistance, and increase in right ventricular work may result (Macklin and Macklin).

Karsner[21] states that pulmonary interstitial emphysema is commonly found in the lungs of children dying with pertussis. Feyrter,[22] in a review

of 100 cases of pertussis which came to autopsy, stated that alveolar rupture was noted and that pneumothorax and interlobular emphysema in the periphery of both lungs was frequently found. Subpleural, mediastinal, and subcutaneous emphysema have been reported in pertussis (Sauer[23]) indicating a probably much higher incidence of pulmonary interstitial emphysema.

Hyperexpansion of the chest with large amounts of bronchiolar exudate and marked respiratory difficulty was noted in each of the cases which showed myocardial insufficiency. Chest roentgenograms revealed diffuse patchy infiltration and focal atelectasis with generalized emphysema in each. Large emphysematous blebs were noted by roentgenogram at the height of myocardial inefficiency in J. T. and a small right-sided pneumothorax was noted by roentgenogram three days before death in G. C. At autopsy, the lungs of G. C. revealed marked emphysema, bronchiolar obstruction by exudate, focal atelectasis, interstitial pneumonia, and interstitial emphysema. J. T. apparently developed a compensated respiratory acidosis, indicating severe obstructive disease. It thus seems quite probable that extensive pulmonary interstitial emphysema was present in each case. It is also logical to assume that the vascular compression consequent to this pulmonary interstitial emphysema could have produced a significant increase in the resistance of the pulmonary circuit. As the normal diastolic pressure in the pulmonary circuit is only 4 to 8 mm. Hg, such an increase in pulmonary peripheral resistance could readily produce a major increase in right ventricular work.

The presence of anoxia, emphysema, and pulmonary interstitial emphysema in association with electrocardiographic changes typical of right ventricular stress strongly suggests that the manifest right ventricular insufficiency was consequent to pulmonary hypertension. Friedberg[13] has pointed out that the elevation of right intraventricular systolic pressure consequent to an increase in pulmonary peripheral resistance may interfere with the coronary drainage into the right ventricle. He postulates that this mechanism may partially account for the myocardial ischemia which appears to be present in acute and chronic cor pulmonale. Wood[19] feels that the strain of excessive work in acute cor pulmonale can account for myocardial injury without postulating a coronary ischemia. In either case when superimposed upon the increased cardiac work necessitated by anoxemia, fever, and severe paroxysmal coughing, such myocardial injury might readily produce clinical cardiac failure.

DISCUSSION

The extended course of the myocardial injury in these cases is worthy of note. In J. T. an abnormal response to liver compression, indicating right ventricular insufficiency, persisted for five weeks. Radiologic evidence of cardiac enlargement persisted for at least five months and electrocardiographic changes indicative of myocardial injury continued for six weeks. Manifest failure recurred several weeks after clinical recovery. It is thus apparent that severe myocardial injury can result from this syndrome which warrants prolonged convalescent care.

The response of the myocardial insufficiency to therapy in J. T. and G. C. is of extreme practical importance. It is well known that most types of acute

cardiac failure respond poorly to digitalis. However, though in each case the myocardial insufficiency continued to progress, in both J. T. and G. C., digitalization produced immediate improvement in heart rate and liver and lung engorgement. As in the case reported by Thompson,[5] the use of mercurial diuretics in J. T., with consequent decrease in the volume of the extracellular fluid compartment, produced recession of all of the manifestations of myocardial insufficiency. Thus, in view of the therapeutic efficacy of digitalis and diuretic agents in this syndrome, symptomatology suggestive of myocardial injury during pertussis warrants thorough investigation.

Evidence of pulmonary interstitial emphysema, hyperexpansion of the chest, dyspnea, and depression of the diaphragms with apparent enlargement of the liver and spleen has been a frequent complication of pertussis in our experience. As each of the cases of myocardial insufficiency which we have seen has been associated with this condition, it has been exceedingly difficult to distinguish the early manifestations of cardiac failure from the pre-existing pulmonary state. Secondary pulmonary infection, emphysema, and interstitial emphysema accounted for a large portion of dyspnea, tachycardia, râles, cyanosis, and apparent hepatic enlargement and always preceded the development of myocardial insufficiency. However, in addition to the electrocardiographic and radiologic alterations in the heart, venous pressure elevation provided evidence of actual myocardial abnormality. The manifestations of pulmonary interstitial emphysema were mistaken for early signs of myocardial insufficiency in several patients who were subsequently shown to have normal venous pressures.

These reported cases seem to demonstrate a causal relationship between the severe pulmonary complications of pertussis and the development of myocardial insufficiency. In this series signs of cardiac disease appeared only in cases where bronchiolar obstruction, focal atelectasis, and emphysema had been present for one week or more. Marked emphysema, large emphysematous blebs, or pneumothorax were present in each of the cases reported and were noted on histological examination of the lungs of G. C. Macklin and Macklin[20] demonstrated that this clinical pattern is always accompanied by interstitial pulmonary emphysema and clearly showed that this latter condition increases the work of the right ventricle. In J. T. and G. C. the manifestations of pulmonary interstitial emphysema were followed by and fused with manifest cardiac failure, while in E. T. the interstitial emphysema itself dominated the clinical picture and was associated with only minimal evidence of right ventricular dysfunction. Thus, the appearance of right ventricular insufficiency in consistent association with pulmonary emphysema seems to indicate that the cardiac manifestations noted in these children were due to overwork and injury of the right ventricle.

CONCLUSIONS

1. Myocardial insufficiency may be a complication of pertussis.

2. The clinical manifestations of myocardial insufficiency seen during the course of pertussis are associated with the manifestations of pulmonary interstitial emphysema and may be consequent to the right ventricular stress occasioned by this condition.

REFERENCES

1. Ledbetter, P. V., and White, P. D.: Effect of Pertussis on the Heart, J. A. M. A. **84**: 1022, 1925.
2. Pfaundler, M., and Schlossman, A.: The Diseases of Children, Philadelphia, 1908, J. P. Lippincott (English translation by Shaw and LaFetra), vol. 2, p. 471.
3. Herman, C., and Bell, T.: A Study of Three Hundred Cases of Pertussis in a Hospital, Arch. Pediat. **41**: 13, 1924.
4. Chajes-Rosenbund, F.: Increase in the Size of the Heart of Children With Pertussis, Ztschr. f. Kinderh. **46**: 55, 1928.
5. Thompson, A. R.: Congestive Heart Failure in Pertussis, Brit. J. Child. Dis. **34**: 273, 1937.
6. Fanconi, G., and Frischknecht, W.: Tachycardia in Pertussis, Helvet. paediat. acta **5**: 2, 1950.
7. Rizzo, N. D.: Pertussis in Infancy, J. PEDIAT. **33**: 300, 1948.
8. Hussey, H. H., and Jeghers, H.: Practical Consideration of Venous Pressure, New England J. Med. **237**: 21, 1947.
9. Winsor, T., and Burch, G. E.: Use of the Phlebomanometer, Am. Heart J. **31**: 387, 1946.
10. Saphir, O., and Amromin, G. D.: Myocarditis in Instances of Pneumonia, Ann. Int. Med. **28**: 963, 1948.
11. Thomson, K. J., Rutstein, D. D., Tolmach, D. M., and Walker, W. H.: Electrocardiographic Studies During and After Pneumococcal Pneumonia, Am. Heart J. **31**: 565, 1946.
12. Saphir, O., and Gore, I.: Myocarditis and Acute Tonsillitis, Am. Heart J. **34**: 851, 1947.
13. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1950, W. B. Saunders Co., p. 546.
14. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, Am. Heart J. **33**: 14, 1947.
15. Musser, J. H.: Medical Diagnosis. ed. 6, Philadelphia, 1913, Lea & Febiger, p. 471.
16. Yeomans, A., Porter, R. R., and Swank, R. L.: Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion, J. Clin. Investigation **22**: 33, 1943.
17. Beck, C. S., and Holman, E.: The Physiological Response of the Circulatory System to Experimental Alterations I, II, III, J. Exper. Med. **42**: 661, 1925, and J. Clin. Investigation **3**: 283, 1926.
18. Fineburg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle. Am. Heart J. **11**: 255, 1936.
19. Wood, P.: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography, Brit. Heart J. **3**: 21, 1941.
20. Macklin, G. L., and Macklin, J. T.: Malignant Interstitial Emphysema of the Lungs and Mediastinum as an Important Occult Complication in Many Respiratory Diseases and Other Conditions, Medicine **23**: 281, 1944.
21. Karsner, H. T.: Human Pathology, ed. 7, Philadelphia, 1949, J. P. Lippincott Co., p. 502.
22. Feyrter, F.: Pathologische Anatomie der Lungen veränderungen beim Keuchhusten, Frankfurt Ztschr. f. Path. **35**: 213, 1927.
23. Sauer, L. W.: in Brennemann's Practice of Pediatrics, Hagerstown, Md., 1948, W. F. Prior Co., vol. 2, chap. 34, p. 15.

UMBILICAL HERNIA

I. Occurrence of the Infantile Type in Negro Infants and Children

E. Perry Crump, M.D.
Nashville, Tenn.

THE benignity of umbilical hernias in infants, the tendency toward a more or less complete disappearance of the defect as the child grows older, and the fact that its existence carries no implication of propensity to congenital anomaly, have seemed to combine to withdraw serious consideration from the condition. The unusually high frequency of umbilical hernia in Negro infants and small children, however, has served to sporadically focus attention in this direction long enough to emphasize the relative rarity with which the abnormality is observed in white subjects.

It is the purpose of this discussion to briefly review some of the few available contributions to the subject, and to present data from observations made on infants and children in the Nashville metropolitan area relative to the sex and age incidence of umbilical hernias in Negroes.

For purposes of classification,[1] three forms of umbilical hernias are usually recognized:

1. Congenital—due to faulty union of the visceral plates in the middle line.
2. Infantile—occurs soon after birth due to yielding of the umbilical cicatrix, after separation of the umbilical cord.
3. Adult—occurs later in life, e.g., women who have borne many children.

The present discussion is concerned primarily with the infantile type.

Jones[2] called attention to the fact that umbilical hernia is seen with far greater regularity in Negro infants than in whites. He indicated that this was true at the Boston Lying-In Hospital, even though Negro and white infants enjoyed the same benefits in prenatal and postnatal care. Moreover, the management of the cord was identical. His estimate that umbilical hernia occurred in about 90 per cent of Negro children presenting at his clinic (Hubbard Hospital) was doubtless too high. He quotes Smith, of Freedman's Hospital in Washington, D. C., who found that of 999 Negro infants* and preschool children examined, umbilical hernia was observed in 58.8 per cent of the former, and 15.7 per cent of the latter.

Evans[3] studied a large number of "colored" and white infants at two health centers in Cleveland, Ohio. All subjects were 1 year of age or less. Of 1,339 colored infants, 24.7 per cent revealed umbilical hernias, while only 3 per cent of 798 white infants were similarly affected. A careful search of the literature has failed to reveal any similar study for purposes of comparison. Except for Smith's reference to the preschool child, no data could be found pertaining to the frequency of hernia in children beyond the period of infancy.

From the Department of Pediatrics, George Hubbard Hospital of Meharry Medical College.

Read before the Section on Pediatrics at the Annual Meeting of the National Medical Association in Philadelphia on Aug. 21, 1951.

*Under 1 year of age.

O'Leary[4] could find only sixty-two umbilical hernias in 80,000 admissions to the University of Oklahoma Hospital during an eighteen-year period. Of these sixty-two cases, only twenty-two were of the infantile type. Albeit, no classification of the infantile type hernia was made as to racial distribution, the data assert the presumption that few Negro infants and small children were represented in the large group of hospital admissions.

Jaffe[5] referred to 150 cases of umbilical hernia in infants and children, and stated that the majority of the children were more or less undernourished and of the plebeian class. Many of these children had family histories of hernia in one or both parents. According to him, the prevalence of hernia in general is far greater among the European masses than in Americans, due to factors of undernutrition, poor hygiene, and inadequate medical attendance at birth, in the former.

ETIOLOGY

A great many causes have been advanced to explain the excessive frequency of umbilical hernia in the Negro infant and small child. High on the heterogeneous list of indictments are rickets, malnutrition, colic and constipation, excessive crying, poor natal and postnatal care, phimosis, etc.

Iason[6] suggests that the main factors appear to be poor natal or postnatal care of the umbilical cord, and rickets. He lists five areas on the posterior surface of an umbilicus where herniation can take place: "... into the umbilical vein, into one of the umbilical arteries, into the urachus, or directly in the center of the umbilicus through the thinned-out fascia of Richet."

Rickets, so commonly cited heretofore, could hardly be currently considered an important cause, inasmuch as the hernia has usually appeared before the infant reaches the age at which rickets is prevalent. In addition, whereas clinical rickets has become relatively rare in our experience, the high frequency of the umbilical defect remains undisturbed. Moreover, no variation in the incidence of umbilical hernia has been observed in relation to such socio-economic factors as might influence dietary adequacy.

Carter[7] cites Moschowitz who regarded the pathogenesis of umbilical hernia as similar in detail to other types of abdominal hernia that occur through openings in the coverings of the abdomen, which are made by structures passing from within the transversalis fascia outward. The herniation usually occurs through the superior quadrant of the umbilical aperature, through which the umbilical vein passes to join the falciform ligament. The protruding sac is lined by peritoneum and is covered by greatly attenuated transversalis fascia, attenuated superficial fascia, subcutaneous fat, and skin.

Mahorner[8] indicates that the underlying causes of the high incidence of umbilical hernia in the Negro are probably absence of the umbilical fascia in a higher percentage of Negroes than in the Caucasian race. He refers to the observations of Gorelow who found the umbilical fascia deficient in 40 per cent of 300 bodies studied, and suggests that this deficiency of fascia permits the development of umbilical hernia much more readily when other etiological factors appear.

The predilection of Negroes to herniation at the umbilicus attests the sig-

FIG. 1.—*A*, *F*, *G*, and *H*, From *Afrika* by Von Ernst Fuhrmann. *B* and *E*. From *Primitive Negro Sculpture* by Paul Guillaume and Thomas Munro, copyright, 1926, by Thomas Munro; used by permission of Harcourt, Brace & Co., Inc. *C* and *D*. From *African Negro Sculpture* by James Johnson Sweeney, The Museum of Modern Art, New York.

Fig. 1 (Cont'd).—For legend, see opposite page.

nificance of racial background, suggests the importance of heredity, and implies the possibility of a familial predisposition. Observations already made in another phase of the present study support the latter implication.

Several years ago, a pathologist from the Belgian Congo, on a brief visit to Hubbard Hospital, related that the presence of umbilical hernia in the African natives is a frequent observation. With this in mind, the Fisk University collection of literature on African art and sculpture was consulted to determine to what extent the umbilical defect had been appreciated and copied by those concerned with the artistic reproduction of body form and contour. Fig. 1 not only presents various tribal subjects with large hernias, but also reveals decorative scarring surrounding the defect, and would seem to suggest that these hernias are regarded as valuable for ornamental purposes.

Buford,[9] suggested that some hernial rings, which previously have been closed, may be reopened by increased abdominal pressure caused by excessive coughing in bronchitis and pertussis. He was impressed with the large proportion of patients with umbilical hernia observed in the dispensary as compared with those found in his private practice, and attributed this to prenatal and postnatal malnutrition, with consequent digestive disturbances and excessive crying.

Wakeley,[10] in 1930, called attention to the increase in the incidence of umbilical hernia during the previous 20 to 30 years. He attributed this to:

(a) More artificial feeding, predisposing to disturbances such as flatulence, distention and constipation, and

(b) Traction on the cord at the time of birth, or within one week after birth.

Baty and Wagner[11] state that umbilical hernias often develop in infants with cutis navel, a congenital anomaly in which the skin overlaps the umbilical cord to a varying length.

Aside from observations suggesting a basic anatomical deficiency in the supporting fascial framework of the umbilicus in Negro infants, no other fundamental or substantial explanation is at hand. One is struck by the high frequency of umbilical hernia in the presence of cretinism[12, 13] and by the reportedly large numbers of premature infants who display the defect, even among white subjects. Wilkens[13] indicates that poor muscle tone is observed as a consequence of decreased thyroid function, and that this is often responsible for a large protuberant abdomen with umbilical hernia. The additional propinquity or common factor in the cretin and premature infant is apparently a low basal metabolic rate.

Smith[14] states that the infant emerges from a state of presumably low heat production during fetal life to a neonatal period in which standard metabolism appears to be less than that of the adult, and considerably below that of the child. He points out that the metabolism of premature infants tends to be slightly less, in proportion to body surface area, than that of infants born at term, and that this discrepancy is greater in the smallest premature.

METHODS OF STUDY

In the endeavor to insure representative sampling of subjects residing in the community, during the course of this study 979 Negro infants and chil-

dren were examined from the Hubbard Hospital Premature Station, Pediatric O.P.D. and Wards, and from several city well-baby clinics and nursery schools. In addition, 258 children (aged 5 to 16 years) were examined from two local private schools involving all grade levels, from kindergarten through the twelfth grade.

No attempt was made to evaluate hernias in terms of size, duration, course, treatment, etc., the objective being simply to determine the presence or absence of the abnormality according to sex and age.

The hernia was considered absent when no patent umbilical defect or umbilical protrusion could be demonstrated, or when a ring, though patent, was immediately reinforced below by a firm resistant structure providing protection and support against herniation or protrusion. This latter condition was classified as a plastic residual of a previous hernia which had undergone adequate resolution.

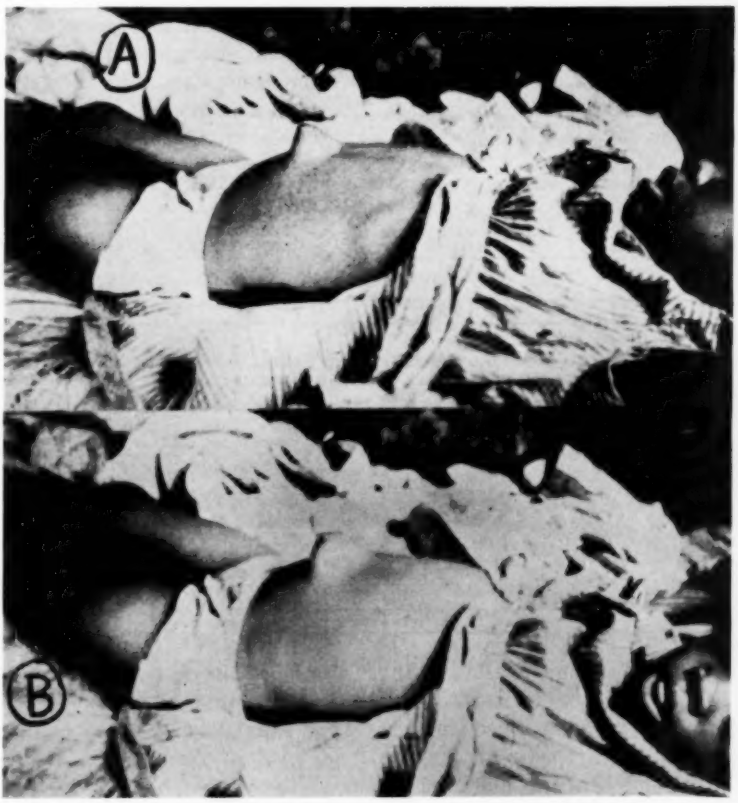


Fig. 2.—*A*, Large hernia with ring measuring 2.8 cm. in diameter. *B*, Effect of increased intra-abdominal pressure (coughing).

A hernia was considered present when the patent umbilical defect permitted protrusion of intra-abdominal structures into the cleft, or allowed the exploring finger tip to advance with facility into the space of the abdominal cavity. Ofttimes, a history of recent umbilical bulging with straining at stool, crying, or coughing was accepted as supporting evidence suggesting the presence of a hernia. In questionable or borderline cases, it was found advantageous to foster an increase in intra-abdominal pressure through the precipitation of crying or mock coughing. In these cases, the rhythmical or synchronous appearance of a bulging mass at the umbilical site, and in many instances the demonstration of crepitation in the protuberance, determined conclusively the presence of a hernia (Fig. 2).

INCIDENCE

A total of 1,237 subjects were examined, and of this group, 329 or 26.6 per cent demonstrated umbilical hernias. For the sake of convenience, the cases were first divided into two major groups. Group I consists of subjects with a birth weight of 2,500 grams or less, and is comprised principally of infants included in the Hubbard Hospital Premature Program. Group II contains those infants and children whose birth weights classify them as full-term (Table I).

The influence of age level on the frequency with which umbilical hernia can be demonstrated in premature infants is immediately apparent, for a difference of 26.2 per cent is to be found between those of less than 1 year of age and those of 1 to 2 years. There is no suitable explanation available for this tendency of the premature infant to rapidly repair the hernial defect in the ventral abdominal wall. Immaturity might be cited as a possible underlying factor, for obviously the hernia tends to close with advance in age. Relatively recent work, however, by Christie,[15] Anderson,[16] and others[17] would seem to challenge this possibility, inasmuch as these investigators have published data on observations suggesting that pound for pound, the

TABLE I. FREQUENCY OF UMBILICAL HERNIA IN PREMATURE INFANTS BY AGE (GROUP I)

AGE	NUMBER		PER CENT
	CASES	WITH HERNIA	WITH HERNIA
Less than 1 yr.	97	44	45.4
1 to 2 yr.	26	5	19.2
Totals	123	49	39.8

TABLE II. FREQUENCY OF UMBILICAL HERNIA ACCORDING TO AGE (NONPREMATURE SUBJECTS—GROUP II)

AGE	NUMBER		PER CENT WITH
	CASES	WITH HERNIA	HERNIA
Less than 1 yr.	437	182	41.6
1-2 yr.	235	67	28.5
3 yr.	82	13	15.9
4 yr.	44	7	15.9
5 yr.	54	5	9.3
6 yr.	56	3	5.4
7 yr.	48	3	6.3
8-16 yr.	158	0	0.0
Totals	1,114	280	25.1

Negro infant is more mature than the white. These views, of course, are not easily reconciled with the common observation that the incidence of umbilical hernia in the Negro infant far surpasses that observed in white infants, regardless of degree of maturity.

eleven were children above 4 years of age. Even more striking is the fact that no instance of hernia was observed in a child above 7 years of age (Fig. 3).

It was to be expected that the frequency of hernia in the premature

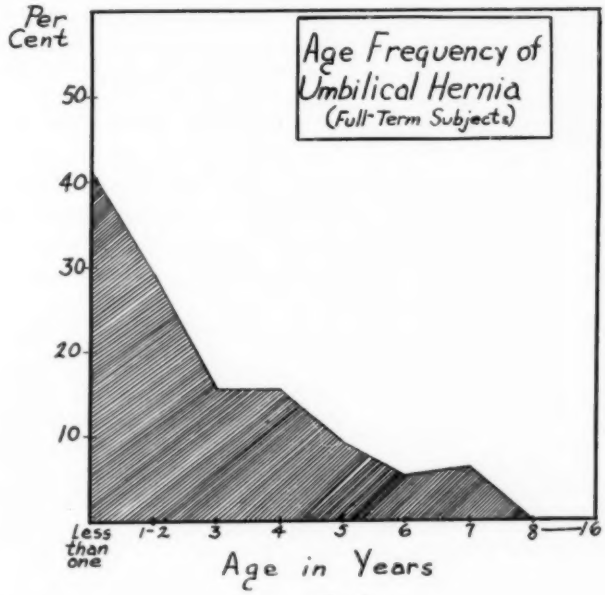


Fig. 3.

Dunham[17] cites Ylppö who found that premature infants were more frequently subject to hernia than full-term infants, and that the incidence was greater the smaller the infant. Hess and Lundeen[18] state that more than 70 per cent of premature infants develop umbilical hernia of sufficient size to require early attention.

This same tendency toward closure of the hernial defect with advance in age is observed in infants and children with full-term backgrounds (Table II).

It is of significance that, of 280 hernias discovered in this group, only

would be higher than in full-term infants. In this study, however, the incidence of umbilical hernia was not significantly higher in premature infants than in the nonpremature group, and it is to be noted that after the first year of life the hernial defect disappeared more rapidly in the former. The number of premature infants under consideration is not large, and for this reason no conclusions, based on these observations, seem justified.

SEX

Of 1,237 subjects examined, the following sex distribution was observed (Table III).

TABLE III. FREQUENCY OF UMBILICAL HERNIA ACCORDING TO SEX

	TOTAL CASES		WITH HERNIA	
	NUMBER	PER CENT	NUMBER	PER CENT
Males	617	49.9	156	25.3
Females	620	50.1	173	27.9
Totals	1,237	100.0	329	26.6 (Average—males plus females)

It is obvious from these data that sex exerted little influence on the frequency of umbilical hernia such as obtains, for instance, in the case of inguinal hernias, where the ratio is eight to ten males to one female.[6]

Barrington-Ward[19] suggests that umbilical hernia is usually found in the female, though he presents no data to display this sexual predominance. He notes that the usual time of appearance is within a few weeks of birth, and indicates that there is a strong tendency to natural cure in these hernias. His experience supports the common observation[1, 7, 12, 20, 21] that incarceration or strangulation is practically unknown in infants and children. Only one such case, a 17-month-old girl, was observed in the present study. She was submitted to operation and recovered uneventfully. Miller,[20] in reviewing all cases of umbilical hernia admitted to the Massachusetts General Hospital for a period of twenty years, found only one case of strangulation in an infant.

Ladd and Gross[21] estimate that umbilical hernias are about twice as common in girls as in boys, and suggest that this is possibly related to the less well-developed musculature in the female.

Jaffe[5] stated that umbilical hernia appears four times as often in females as in males, while Carter[7] maintained that there is no apparent difference in the two sexes. None of these reports is supported by specific data on sex frequency.

SUMMARY AND CONCLUSIONS

1. A total of 1,237 infants and children were examined to ascertain the age and sex frequency of umbilical hernia in Negro subjects. Of this group, 329 or 26.6 per cent revealed the defect.

2. This umbilical abnormality was observed somewhat more commonly in the young premature infant than in subjects with full-term backgrounds, but the difference is of a smaller order of magnitude than anticipated. The relatively small number of infants examined in the premature group might explain the latter observation.

3. Sex exerted no significant influence upon the frequency of umbilical hernia, inasmuch as females exceeded males by only 2.6 per cent.

4. Age is of decisive import, for the incidence of the umbilical defect varies inversely with the age of the subject. It is found very frequently during the first year of life, but was not found in a single instance in children above 7 years of age. Of all cases studied, the condition occurred in 42.3 per cent of those less than 1 year of age, and in 27.6 per cent of those between 1 and 2 years of age.

5. The many conditions commonly cited as causes of umbilical hernia in infants and children attest the existing

confusion and uncertainty regarding the fundamental etiological basis for the condition.

6. The defect carries a strong racial predisposition, and probably occurs about eight times more frequently in Negroes than in whites. There is evidence at hand also to indicate a familial predilection for the condition.

7. The fact that a low basal metabolic rate is associated with conditions in which umbilical hernia is commonly found (eretinism and prematurity) suggests that this factor may be related. Experimental studies are under way at present to test the significance of this observation.

REFERENCES

1. Coley, Bradley L.: The Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, 1939, F. A. Davis Co., vol. VII, pp. 257-258.
2. Jones, J. W.: The Frequency of Umbilical Herniae in Negro Infants, Arch. Ped. **58**: 294, 1941.
3. Evans, Armen G.: The Comparative Incidence of Umbilical Hernias in Colored and White Infants, J. Nat. Med. Assoc. **33**: 158, 1941.
4. O'Leary, Charles M.: Umbilical Hernia, Am. J. Surg. **52**: 38, 1941.
5. Jaffe, N. B.: Umbilical Hernia, Rev. Gastroenterol. **14**: 562, 1947.
6. Iason, Alfred H.: Pediatric Progress, Philadelphia, 1948, F. A. Davis Co., pp. 389 and 455.
7. Carter, Franklin R.: Umbilical Hernia: Types and Treatment, Arch. Ped. **49**: 622, 1932.
8. Mahorner, Howard: Umbilical and Midline Ventral Herniae, Ann. Surg. **111**: 979, 1940.
9. Buford, Coleman C.: Umbilical Hernia of Infants and Children, S. Clin. Chicago **2**: 633, 1918.
10. Wakeley, Cecil P. G.: Umbilical Hernia in Infants and Its Treatment, Lancet **2**: 309, 1930.
11. Baty, James M., and Wagner, Richard: The Child in Health and Disease (Grulee and Eley), Baltimore, 1948, Williams & Wilkins Co., p. 585.
12. Mitchell-Nelson: Textbook of Pediatrics, ed. 5, Philadelphia, 1950, W. B. Saunders Co., p. 1384.
13. Wilkens, Lawson: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas Publisher, p. 70.
14. Smith, Clement A.: The Physiology of the Newborn Infant, Springfield, Ill., 1950, Charles C Thomas Publisher, p. 175.
15. Christie, Amos: Prevalence and Distribution of Ossification Centers in the Newborn Infant, Am. J. Dis. Child. **77**: 360, 1949.
16. Anderson, Nina A., Brown, Estelle W., and Lyon, R. A.: Causes of Prematurity. III. Influence of Race and Sex on Duration of Gestation and Weight at Birth, Am. J. Dis. Child. **65**: 523, 1943.
17. Dunham, Ethel C.: Premature Infants—A Manual for Physicians, Children's Bureau Publication No. 325, p. 214, 1948.
18. Hess, Julius H., and Lundeen, Evelyn C.: The Premature Infant, ed. 2, Philadelphia, 1949, J. B. Lippincott Co., p. 272.
19. Barrington-Ward, Sir Lancelot: The Hernia Problem in Children, Practitioner **159**: 379, 1947.
20. Miller, Richard H.: Umbilical Hernia, New England J. Med. **206**: 389, 1932.
21. Ladd, William E., and Gross, Robert E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1948, W. B. Saunders Co., p. 325.

A PEDIATRIC RESIDENT PROGRAM IN A NONUNIVERSITY HOSPITAL

H. E. THELANDER, M.D.
SAN FRANCISCO, CALIF.

AN EXPLORATORY study of the nonuniversity hospital as a training place for residents who intend to practice pediatries was undertaken three years ago. Many hospitals not connected with medical schools have no paid faculty and any teaching that is done must be by volunteer doctors. Can such a hospital offer adequate training to a young physician? What services are necessary? How should the program be arranged? How long does it take to master a subject such as allergy sufficiently to have a working knowledge of it? These were some of the questions we sought to answer.

Advanced training, such as for a specialty, is dependent on the preparatory education. Even though all the residents come from class A medical schools, they show variation in training more than that due to inherent ability. In general, all are accustomed to work directly with patients and show remarkable technical skill. Most of them still think chiefly in terms of the interesting case with little or no orientation in psychiatry or sociology. Only a few have some concept of growth and development.

At the start of the study members of the resident staff were asked to outline a desirable two-year service. This, and the staff's personal experience in the demands of practice, formed the basis for the revised program.

From the Department of Pediatrics, Children's Hospital.

Children's Hospital in San Francisco is particularly fortunate in having, in addition to its pediatric ward, a communicable disease department, a child guidance center, active surgical and orthopedic divisions, a large maternity service, and an outpatient department. With these basic units in mind the services have been divided as follows:

First year: Six months on the communicable disease division; six months in the outpatient department and child guidance, time being approximately equally divided between the latter two.

Second year: Six months in medical pediatries and six months in surgical pediatries combined with the newborn and premature nurseries.

Since preparation for practice was the goal set for our training program, the following details of the various services have been instituted:

1. In order to prepare for that part of practice which deals with the newborn and infant, the resident examines all newborn and premature infants, holds group discussions with mothers on dismissal from the hospital to answer questions, and participates in the well-child clinic. The resident attends cesarean sections, and difficult or premature deliveries, assuming responsibility for proper resuscitation. At the beginning of the training period, methods and techniques of resuscitation are reviewed jointly by the obstetric and pediatric staffs.

One hour weekly after the well-child conference members of the staffs of child guidance and pediatrics meet to discuss the normal child, his growth and development and the impact of the environment upon him. The discussions open at the beginning of the resident year with the details of examination of the newborn infant, types of defects encountered, telling parents about defects, prenatal education, rooming-in, breast feeding, and questions that are raised by new mothers. There is a rough budgeting of time but in general as many sessions are spent on a given age period as are needed to clarify the questions raised. The discussions proceed to the age of training and the problems associated with it, the nursery school years, the school age, and finally adolescence. An effort is made to cover all aspects, the physical growth, mental and emotional development, and socialization of the young. Members of other disciplines, namely, education, religion, sociology, anthropology, and recreation are freely called upon to participate at different times.

2a. In order to prepare for office practice other than infant care, the outpatient clinics have been set up to simulate an office. Visits are made by appointment and the resident has responsibility for diagnostic and therapeutic measures. The senior physician in charge of a given session reviews these practices with the residents, acts as consultant, and sees patients if the day is crowded. Experience is gained in the proper management of consultations, referals, hospitalization, and follow-up of patients.

To supplement this training a seminar on practical pediatrics is held once weekly. It was felt by the staff that there were two neglected areas in pediatrics to which residents could be oriented by group discussion. One of these concerns the "trivia" of practice, many samples of which the resident is now encountering in the clinic. The other is the area that abuts a speciality but the problems of which are usually brought first to the pediatrician, namely, conditions like strabismus, feet and hip deformities, speech and reading problems.

b. The child guidance center gives the residents not only the benefit of group discussions and conferences but actual experience in interviews with patients, both parents and children. Six months is probably the very minimal for proper orientation in child psychiatry.

3. The care of the acutely ill patient as well as experience in difficult diagnostic problems is obtained on the three ward services—pediatrics, surgical pediatrics, and the communicable disease division.

a. A private nonuniversity hospital provides a larger proportion of acutely ill patients and fewer diagnostic or chronic problems although an appropriate number of these are seen also. An attempt is being made to supplement the resident's training by building up visual aids in the form of slides, pictures, and reprints of the unusual cases. The Journal Club this year is also spending part of its time in the review of certain rare and unusual diseases.

b. The teaching of surgical pediatrics is left almost entirely to the surgical staff. It is supplemented by the bedside rounds in which the child guidance and pediatric staffs participate. The service includes eye, plastic work, ear, nose and throat, orthopedics,

and general surgery. It gives the resident experience in pre- and postoperative care, types and management of anesthesia, and the emotional problems raised by surgery. It is an excellent place to study fluid balance and it particularly adds to the experience of learning techniques from other specialties such as the use of the ophthalmoscope, nasal examination, etc.

c. The communicable disease division in a private hospital also differs from that in a county hospital, having more acute and less chronic problems. It offers the most emergencies and the greatest number of unusual techniques. On this service enter the cases of fulminant meningococcic sepsis, the patients in need of tracheotomy, the respiratory failures, the poliomyelities with inability to swallow, and the unconscious patient from whatever cause. The service provides excellent experience in rapid differential diagnosis, the selection of diagnostic procedures that will accomplish this and at the same time permit speedy institution of the best therapy to avoid a fatal outcome. There is probably no other service that tests judgment in face of an emergency as does this service.

These ward services are supplemented by bedside rounds once weekly in which nurses, social workers, pediatricians and psychiatrists participate. Once weekly formal rounds are held with detailed study and discussion of cases. Both of these rounds are rotated through the different pediatric services. Once a month one of the hours is spent on the discussion of fatal cases and once a month the tumor board meets.

The rounds and seminars are distributed through the week so that usually only one hour a day, near the noon period, is devoted to such activity. Teaching time is distributed among many pediatricians on the staff and the individual burden therefore is not great.

4. Other experiences valuable to a practicing physician are interspersed with the above activities. The social service department arranges several field trips to children's institutions during the year. Experience in public speaking and teaching is gained by the group talks to mothers, the case presentation at rounds, and participating in lectures to the nurses. Each resident pursues a project during the stay at the hospital which involves review of literature, the study of cases, keeping a bibliography, etc. Some of these may be published in the original or revised form, or if this is not done, they are bound in a Manila cover and placed in the library. This brings dead record room material into readily available form.

The residents are urged to have a Journal Club and to participate in the Junior Pediatric Society.

5. One of the deficiencies in this program has been the lack of adequate experience in the subspecialties of pediatrics. The patients acutely ill with rheumatic fever or an allergic condition will be seen on the wards, and some time has been taken from both the house and the outpatient services to devote to the specialty clinics; but there is no time actually set aside for undivided application to these clinics for a long enough period of time to grasp the fundamental principles and integrate them into practice. For this reason a third-year residency in pediatrics will be attempted. The work will consist of attendance at the following weekly specialty clinics: allergy, car-

diology, neurology, endocrinology, and hematology. The other half of the day, these being half-day sessions, offers opportunity for the resident to select a variety of pediatric activities and therefore a chance to supplement deficiencies in training. There is available pathology, x-ray, school health, other specialty clinics—notably dermatology, orthopedics, rehabilitation of the poliomyelitic patient, prenatal, and ear, nose, and throat clinics. This should be a very valuable training period.

This is an exploratory program. Each year the residents are asked to give an evaluation of the different activities, and alterations have been made on this basis. A questionnaire is also sent to those recently entering practice from our school to get their evaluation and suggestions.

The program is presented at this time in order to enlist the faculties of other nonuniversity hospitals in study and discussion of the original training as well as the maintainance of interest in learning of practicing physicians. The field of pediatrics, since its delineation as a specialty, has expanded in scope to include everything from cardiology to child guidance and there is not much likelihood that it will change in character in the foreseeable future. In planning a resident program, therefore, not only the content must be considered, but also the length of time of application to a given facet of pediatrics to gain a working knowledge of it. In part this depends upon the emphasis that has been given a subject during the undergraduate years and in part on the ease with which experience can be gained after formal training has ceased. The latter in turn is dependent upon location and the availability of clinic appointments. Probably a better understanding of a disease such as diabetes or rheumatic fever is gained by following a few patients weekly for a year than by seeing many patients daily for two or three months. Some problems of education that need elucidation are: (1) The preferable order in which the training should be presented to the resident. (2) The optimum time to devote to a single facet to be proficient enough to pose as a specialist when formal training is over. (3) The total time of training under maximum efficiency (is two years adequate?). (4) The methods of training at this stage—should it be entirely bedside, or is there a place for seminars, discussion groups, or even didactic lectures? Are these latter methods more welcome at this stage of synthesis of knowledge than during the undergraduate years? (5) How can service to the patient and education of the doctor be combined without exploiting either? (6) In private and semiprivate hospitals, shall the cost devolve on the private patient; if not, who shall pay for it? (7) Are practicing pediatricians interested in carrying on an educational program on a volunteer basis, or is this expecting too much?

SUMMARY

An attempt has been made to organize the material in a nonuniversity hospital in such a manner that a resident in training would have the opportunity and sufficient undivided time to explore the different facets of pediatrics so that he would be properly oriented in each when he enters the practice of his specialty.

DERMATITIS GANGRENOSA INFANTUM

LIEUTENANT ALBIN GEDAROVICH, MEDICAL CORPS, UNITED STATES NAVY

DERMATITIS gangrenosa infantum is a gangrenous dermatitis which occurs in young children following the exanthematous diseases or independently. Most of the cases reported in the literature have occurred in infants and children below the age of 3 years. Reference to a case occurring in the immediate newborn period could not be found. For this reason it was felt that this case should be reported.

CASE REPORT

History and Physical Examination.—On April 8, 1951, a 6 pound 6 ounce white male infant was born at the U. S. Naval Hospital, Bethesda, Md. The labor was of 4½ hours' duration and was uneventful.

On physical examination the infant was noted to have large weeping areas of skin involving the scalp, back of the neck, upper back, buttocks, and scrotum. The rest of the infant's skin had a somewhat waxy feel such as is seen in sclerema neonatorum. The cry was good, and examination of the heart and lungs was negative. Liver and spleen were not palpable. Snuffles, palmar, or plantar dermatitis were not present, and the Nikolsky sign was negative. In view of the possible infectious nature of such a condition the infant was immediately admitted to the isolation nursery until suitable laboratory studies could be carried out.

Perusal of the mother's chart revealed that she was a gravida iii, para i. She had previously given birth to a living child and had had a miscarriage at three months. Her Rh factor was negative and there was no evidence of any anti-Rh antibodies in her blood ten days before delivery. Interestingly enough she had been treated for a vaginitis of unknown etiology shortly before delivery. A sulfa-containing vaginal cream was prescribed, but no bacterial cultures were done at that time.

On admission to the hospital her membranes were intact, and there was only a slight bloody show. Labor progressed satisfactorily, and post-partum inspection of the placenta revealed that there had been a central rupture of the membranes. Adherent to one-fourth of the periphery was a dark red clot which possibly represented an area of premature separation. Her temperature was 100° F. on the first post-partum day, but remained flat for the remainder of her six-day hospital stay.

Laboratory Findings.—Immediately after birth, blood studies revealed that the infant was Rh negative. A Coombs test was negative as was a blood Kahn. The red count was 5.9 million with 17 Gm. of hemoglobin. White blood count was 20,600 with 59 per cent neutrophils, 5 per cent bands, 1 juvenile, 1 myelocyte, 25 per cent lymphocytes, 4 per cent eosinophils, and 4 per cent monocytes. Seven nucleated red blood cells per 100 white blood cells were noted. A blood culture was drawn eight hours after birth.

Course.—Oral feedings were withheld for the first twelve hours. Thereafter glucose solutions were offered by mouth. For the first twenty-four hours the temperature remained persistently subnormal and varied between 97.2° and 97.4° F.

During the next twenty-four hours the infant's condition was noted to have deteriorated markedly. A 20-ounce weight loss had taken place since birth and it was apparent that large quantities of serum were being lost

---

The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval establishment at large.

Present address: U. S. Naval Hospital, St. Albans, N. Y.

through the denuded skin. His cry was weak and his extremities were cyanotic. Along pressure points on the back, buttocks, neck, and head there were noted papules and pustules, many of which had areas of hemorrhage about them.

Three days after birth the temperature began to climb and remained between 101° and 102° F. Definite areas of hemorrhagic necrosis with eschar formation were present over the dorsal surface of the infant's body.

Four days after birth the escharotic lesions increased in extent. Fever continued and the infant passed a grossly bloody stool. Despite intensive therapy he expired.

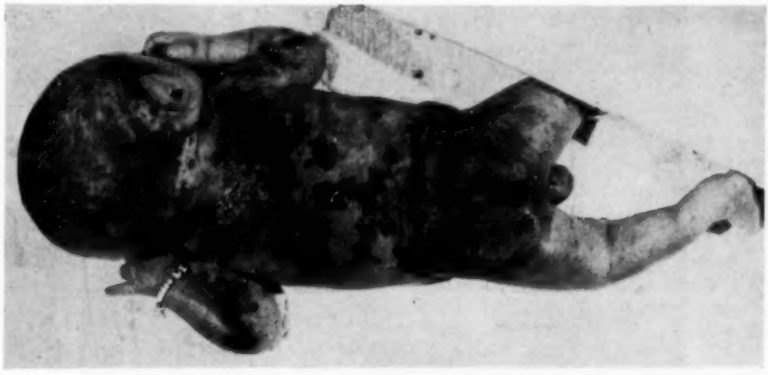


Fig. 1.—Eight hours before death, showing extensive areas of hemorrhagic necrosis.

Therapy.—Initially petrolatum gauze was applied to the oozing areas. Crysticillin was started when a blood culture was reported positive for hemolytic *Staphylococcus aureus*. Later, when he did not appear to be responding favorably, aqueous penicillin 30,000 u. was given intramuscularly, q.3.h., and Chloromycetin was given rectally in a dosage of 50 mg. q.4.h. Applications of Furacin ointment were made directly to the escharotic skin.

Because it became evident quite early in the course that enormous amounts of protein and electrolyte were being lost through the skin, a venous cut-down was done and a No. 20 polyethylene tube was inserted to facilitate fluid therapy. Through this the infant received saline lactate solutions, plasma, and whole blood. Despite this, plasma replacement was inadequate and on the day of death total proteins were reported as 3 Gm. with 2.2 Gm. of albumin and 0.8 Gm. of globulin.

Bacteriology.—The initial blood culture was drawn eight hours after birth. At twenty-four hours no growth was reported, but at forty-eight hours a hemolytic *Staph. aureus* was definitely demonstrated. On the day of death a repeat blood culture again was positive for *Staph. aureus*. Cultures from the skin and hemorrhagic pustules revealed both hemolytic *Staph. aureus* and hemolytic *Staph. albus*. No fungi were ever isolated and stool cultures were negative. Post-mortem blood cultures showed only *E. coli*. Unfortunately no sensitivity studies were done.

Vaginal cultures were not done on the infant's mother ante partum at the time of her original vaginitis. However, six weeks post partum cultures revealed the presence of a hemolytic staphylococcus.

Autopsy.—Post-mortem examination revealed the presence of a generalized hemorrhagic, gangrenous dermatitis. In addition there were hemorrhages

into the colon, adrenal, and stomach. There were slight pulmonary edema, a small subarachnoid hemorrhage in the left cerebral hemisphere, and bilateral uric acid infarcts of the kidneys. No visceral or pulmonary abscesses were found.

Microscopic examination of the skin revealed areas of extensive ulceration with necrosis and marked diffuse hemorrhage throughout the dermis. In some areas there were hemorrhagic vesicles. In others there was basal cell proliferation of the epidermis.

Fig. 2.

Fig. 3.

Fig. 2.—Section of skin, showing diffuse hemorrhage and necrosis throughout the dermis. (×30.)

Fig. 3.—Section of skin, showing loss of epidermis, extensive hemorrhage, and necrosis. (×100.)

Sections of the adrenals showed extensive cortical hemorrhages.

Examination of the esophagus, stomach, and small and large intestines

showed marked hemorrhage throughout the mucosa, submucosa, and muscularis.

DISCUSSION

Considered originally in the differential diagnosis were many of the dermatologic conditions peculiar to infancy. The absence of plantar and palmar lesions as well as a negative Kahn ruled out the presence of syphilitic pemphigus. The absence of a Nikolsky's sign (ability to remove the superficial layers of skin by digital friction) and the presence of the condition from birth tended to rule out Ritter's disease. Likewise, its early inception and the absence of any seborrhea militated against a diagnosis of erythroderma desquamativum of Leiner. Pemphigus congenitus, which is often staphylococcal in origin, could not be accepted fully because bullae were never demonstrated. However, in view of the fact that hemolytic *Staph. aureus* was demonstrated to be present in the blood stream immediately after birth, the conclusion that this organism and the dermatitis were linked together was inescapable. This infant undoubtedly represented an example of intrauterine sepsis, with the mother's vaginitis acting as the source of the infecting organism. At birth the skin displayed lesions suggestive of an eczematous dermatitis with large, raw, weeping areas. Engrafted onto this was the picture of a pyoderma which progressed to a hemorrhagic, then a gangrenous dermatitis.

REVIEW OF THE LITERATURE

Review of the literature reveals reports on this condition dating back as far as 1887, when Crocker[1] discussed etiology and mentioned the incidence of this condition following the then prevalent varicella. He felt that it occurred in weakened infants and that it was due to a microorganism from without.

In primary cases the lesions have been described as starting out as discrete papules which evolve into pustules. These become covered with a scab. Ulceration occurs and then a black eschar which involves the entire thickness of the skin ensues. This sequence was confirmed by Blatt and Stulik[2] who added the additional information that these ulcerations could occur anywhere, and that, as in variola, cutaneous irritation and pressure are the factors which determine localization of the lesions.

Most of the cases reported in the literature have occurred in children below the age of 3 years. Libermann[3] reported four cases in infants, aged 4 months, 8 months, 12 months, and 18 months. Blatt[2] reported a single case in a child 2 years 11 months old. Morrissy[4] reported a 3-year-old. Falcon Garcia[5] reported a 2-year-old. Reference could not be found to a case occurring in the immediate newborn period.

The causative organism in the above-mentioned cases was in each instance either a *Staph. aureus* or a virulent staphylococcus. This is all the more credible when one recalls that the staphylococcus is a potent organism possessed of many varied toxins. One may list a hemolysin, leukocidin, coagulase, fibrinolysin, spreading factor (Duran-Reynals), lethal factor, enterotoxin, and skin necrotoxin.[7] The latter was demonstrated in sterile filtrates of broth cultures in which *Staph. aureus* had been grown by Parker[8] in 1924. When these filtrates were injected intra- or subcutaneously into rabbits it was found that necrosis of skin occurred over a period of days. It is interesting to theorize on the role that this toxin plays in the genesis of the lesions in gangrenous dermatitis, but it is probably combined with other factors such as venous thrombosis as suggested by Liebermann.[3]

Other agents, of course, may occasionally play a role in causing gangrenous dermatitis, and localized instances have been reported following insect bites, bismuth injections, epinephrine injections, typhus, and meningococcemia.

SUMMARY

A case of dermatitis gangrenosa infantum, which occurred in a newborn infant with fatal outcome, is reported. The etiological agent was shown to be the hemolytic *Staph. aureus*. This same organism was cultured from the mother's vagina.

REFERENCES

1. Crocker, H. R.: Brit. M. J. **1**: 1333, 1887.
2. Blatt, M. L., and Stulik, C. K.: Arch. Dermat. & Syph. **38**: 407, 1938.
3. Liebermann, S.: Arch. f. Dermat. u. Syph. **171**: 172, 1935.
4. Morrissy, M. J., and Reynolds, H. S.: Arch. Dermat. & Syph. **22**: 811, 1930.
5. Falcon Garcia, F.: Rev. clin. españ. **28**: 326, 1948.
6. Meneghello, J. R., and Guasch, J.: Rev. chilena pediat. **15**: 1034, 1944.
7. Jordan-Burrows Textbook of Bacteriology, Philadelphia, 1949, W. B. Saunders Co., pp. 348-349.
8. Parker, J. T.: J. Exper. Med. **40**: 761, 1924.

INTOXICATION WITH VERATRUM VIRIDE

ARTHUR J. NEWMAN, M.D.
CLEVELAND, OHIO

VERATRUM viride is emerging from a period of obsolescence and enjoying new popularity as an effective agent for the treatment of hypertension. As a result, intoxications from its use and occasionally the accidental ingestion of this drug may be expected to occur more frequently.

The purpose of this report is to present a case of poisoning with veratrum and to discuss briefly the pharmacologic action of the drug and therapy for its toxic effects.

CASE REPORT

This 23-month-old Negro infant was in good health until fifteen minutes prior to her first University Hospitals admission. One-half hour earlier she had ingested an unknown number of tablets each containing 1 mg. of veratrum viride. The medication had been prescribed for the child's grandmother and the bottle when filled contained 100 tablets. It was not known how many the grandmother had taken, but when found the bottle was only one-third full. The child showed no symptoms for one-half hour and then began to vomit. She became somnolent and was rushed to the emergency ward.

Physical examination on admission revealed a stuporous and critically ill Negro child who became restless on being stimulated and retched violently. Her skin was cool and moist. Temperature was 35.8° C. Eyes showed dilated pupils not reacting to light. Fundi were not visualized. The posterior pharynx was filled with foam and mucus. Respirations were slow, regular, and shallow, 16 per minute. Heart sounds were poor with evident bradycardia of 68 per minute. Blood pressure was 60/0. Neurological examination showed poor muscle tone with absence of all deep tendon reflexes. No abnormal reflexes were elicited.

The child's stomach was lavaged with 1,000 c.c. water. She was given 0.0001 Gm. atropine sulfate subcutaneously and transferred to the ward. Because it appeared that the child was going into shock, an intravenous infusion of 10 per cent dextrose in distilled water was begun. Before 10 c.c. of this solution had run in it was noted that the child's pulse had rather suddenly risen to 144 and the respirations had increased to 27 while the blood pressure rose to 90/60. (Approximately twenty minutes had elapsed between the administration of the atropine and the increase in heart rate.) The intravenous drip was continued till 150 c.c. of the aforementioned dextrose solution and 300 c.c. of a mixture of one-half 5 per cent dextrose in distilled water and one-half Ringer's solution had been absorbed. The child received no further medication. By the following morning, eight hours later, the temperature was 36.8° C., pulse 124, respiration 30, blood pressure 104/60. There were no further manifestations of the intoxication and the child was discharged on the next day.

DISCUSSION

Veratrum viride is obtained from a plant in the lily family known as green hellebore. Its active constituents are alkaloids, the most potent being protoveratrine.[1]

There is some dispute as to its mode of action. Goodman and Gilman[2] feel that the alkaloids act on the vagal nuclei in the medulla. Meilman and Krayer,[3] on the other hand, feel that there exists a vasodepressor reflex pathway having afferent fibers in the

From Babies and Childrens Hospital and the Department of Pediatrics, Western Reserve University School of Medicine.

vagus nerve itself and that "the reflex decrease in heart rate and in blood pressure caused by small doses of veratine originated predominantly in the ventricular myocardium and that the afferent impulses were carried by nerve fibers running in the vagus nerves." Freis and associates[4] suggest a possible effect of dilatation of the postarteriolar vascular bed. Stutzman and collaborators[5] working on Veriloid, the agent in this instance, are mentioned by Loofbourow and Palmer[6] as showing that the fall in blood pressure could be elicited by Veriloid even after vagotomy even though bradycardia could not. They believed that the hypotension was caused by arteriolar dilatation accompanied by constriction of venous vascular beds.

In any event, the effects of administration of the drug include slowing of the heart rate, fall in blood pressure, sweating, and hypothermia. In addition, poisoning is accompanied by nausea, vomiting, diarrhea, headache, and cardiovascular collapse. Because of its pronounced emetic action poisoning is said to be rare. Even when emesis does not occur, the effects of the drug are dissipated in eight or nine hours and no irreversible damage is thought to result.

Death, however, may ensue unless an antidote is used. Atropine, ephedrine, and morphine sulfate are mentioned as antidotes.[6, 7] The hypotension might be expected to remain if atropine alone is used, since only the vagal effects of veratrum are thought to be abolished by atropine. Our patient, however, manifested an increase in blood pressure concomitant with the increase in pulse rate.

SUMMARY

A case of accidental poisoning with veratrum viride is reported. Atropine provided rapid relief of the symptoms in this patient. A brief discussion of the pharmacologic action of veratrum is included.

REFERENCES

1. Sollman, Torald: A Manual of Pharmacology, ed. 7, Philadelphia, 1948, W. B. Saunders Co.
2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Co.
3. Meilman, Edward, and Krayer, Otto: Clinical Studies on Veratrum Alkaloids. I. The Action of Protoveratrine and Veratridine in Hypertension, Circulation **1**: 204, 1950.
4. Freis, Edward D., Stanton, Joseph R., Culbertson, James W., Litter, Julius, Halperin, Meyer H., Burnett, Charles H., and Wilkins, Robert W.: Hemodynamic Effects of Veratrum Viride, J. Clin. Investigation **28**: 353, 1949.
5. Stutzman, J. W., Marson, G. L., and Kusserow, G. W.: Veriloid, New Hypotensive Extract of Veratrum Viride, Proc. Soc. Exper. Biol. & Med. **71**: 725, 1949.
6. Loofbourow, D., and Palmer, R. S.: Hypertension in Medical Progress Section, New England J. Med. **243**: 257-265, 295-307, 1950.
7. Wilkins, R. W.: Veratrum Viride and Essential Hypertension, New England J. Med. **242**: 535, 1950.

ENGELMANN'S DISEASE (PROGRESSIVE DIAPHYSEAL DYSPLASIA)

LEROY S. LAVINE, M.D.,* INDIANAPOLIS, IND., AND
MORRIS T. KOVEN, M.D., BROOKLYN, N. Y.

IN 1929, Engelmann[1] first called attention to an unusual syndrome which was characterized by fusiform expansion and hyperostosis of the diaphyses of the long bones together with wasting and anomalous muscular signs.

This unusual condition was not reported again until 1943, when Riley and Shwachman[2] reported two additional cases, and presented the first microscopic study of the bone lesion. Neuhauser and his co-workers[3] reported two more new cases in 1948. Sear[4] in 1948, Michaelis[5] in 1949, Bingold[6] and Stronge and McDowell[7] in 1950, Gillespie and Mussey[8] and Gulledge and White[9] in 1951, all reported single cases of this syndrome, bringing the total of reported cases to date to eleven.

Thus, from the reports in the literature over a period of more than twenty-two years, one can see that this is either an extremely rare condition or that it is seldom recognized in diagnosis.

It is the purpose of this paper to describe the clinical, roentgenologic, and pathologic features of a new case of progressive diaphyseal dysplasia. We are reporting this case not only because of its rarity but also because of our desire to correlate it with some experimental work which may throw light upon its etiology. We are presenting some additional laboratory data which may likewise prove of interest.

CASE REPORT

K. M., a 12-year-old white male, was admitted to the Jewish Hospital of Brooklyn on June 5, 1950, because of muscular weakness, easy fatigability, and waddling gait.

From the Department of Orthopedic Surgery, Jewish Hospital of Brooklyn.
*Indiana University Medical Center.

In his past history, it is noted that K. M. was brought to the Out-Patient Department in 1944 at the age of 6 years because of tiredness initiated by walking. The patient was diagnosed as a case of third degree pes planus with muscle fatigue on this basis.

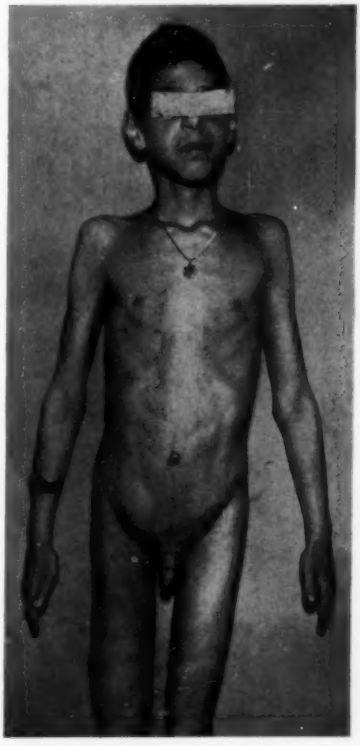
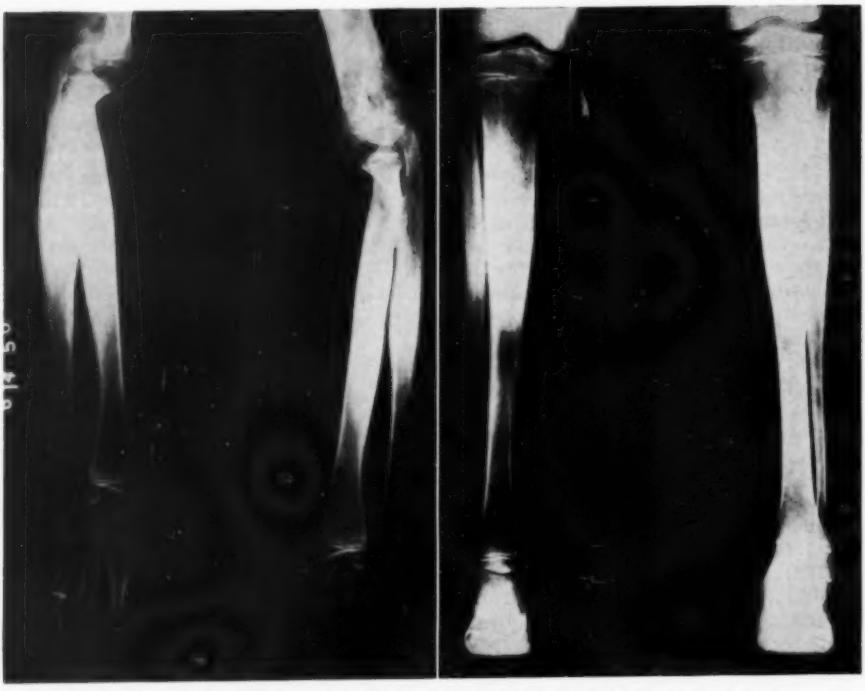


Fig. 1.—Child with Engelmann's disease, showing underdeveloped musculature.

There were no specific complaints regarding the upper extremities. He was referred to the pediatric department for study because of poor nutrition. A high calory diet supplemented by malt with cod-liver oil was pre-



Figs. 2 and 3.—Fusiform expansion and hyperostosis of the diaphyses of the long bones.

Fig. 4.—The skull, showing sclerotic thickening of the base.

scribed. An examination two months later revealed that his appetite was still poor.

In 1946, at the age of 8 years, a tonsillectomy was performed without any complications.

In 1947, the patient had a pediatric neurological consultation. The diagnosis at this time was changed to an early muscular dystrophy. There was no additional follow-up until the present hospital admission.

Family history revealed that the child's father died of tuberculosis and his mother is, at present, confined to a tuberculosis sanitarium.

No restriction of motion in joints adjacent to the bony areas was apparent. Although muscle tone was diminished, resistive muscle power was good. The patient's deep tendon reflexes were hyperactive.

No abnormality of the visual fields was found and electroencephalography was normal. Psychological testing showed the patient's intelligence to be in the low normal or dull category.

Laboratory findings were as follows: Mazzini and Wassermann tests were negative. Urinalysis was normal; Bence-Jones protein was absent. A tuberculin test was positive to 0.1 mg.

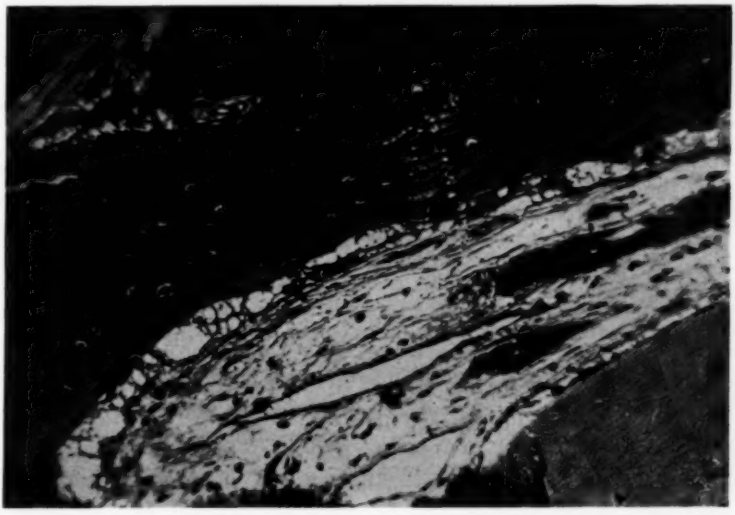


Fig. 5.—Photomicrograph of biopsy specimen, showing broad, dense, bony trabeculae, and fibrotic marrow.

Physical examination upon this admission showed a slender, malnourished boy who measured 58 inches in height and weighed 62 pounds. No abnormalities were apparent in either the head or neck. The upper and lower extremities were long in proportion to a narrow torso. There were no spinal or chest deformities. Through a sparse musculature, one could palpate nontender symmetrical areas of bone thickening in the shafts of the femora and tibiae.

Complete blood count on four different occasions was normal with the sedimentation rate at 22 mm. per hour.

Chemical analyses were as follows: Calcium, 10.8 mg. per 100 ml. serum; phosphorus, 4.3 mg. per 100 ml. serum; alkaline phosphatase, 6.9 Bodansky units; total protein, 7.7 Gm. per 100 ml serum; albumin, 4.0 Gm.; globulin, 3.7 Gm.; total cholesterol, 205 mg.; free cholesterol, 6.2 mg.; urea nitrogen, 13 mg.; uric acid, 3.3 mg.; sugar, 80 mg.; chlorides, 370 mg.; sodium,

331 mg.; potassium, 22.1 mg.; CO_2 content, 56.3 volumes; vitamin C, 0.94 mg.; vitamin A, 67 μg; carotenoids, 113 μg per 100 ml. plasma; vitamin A tolerance test, range from 187 to 342 per cent when 6,000 units of oleum percomorph were given; electrophoretic blood curve was within normal limits.

X-ray studies of the femora, tibiae, humeri, radii, ulnae, skull, and jaw were made. The chief finding in these x-rays was a symmetrical skeletal distribution with fusiform enlargement of the diaphyses of the shafts of the long bones. The epiphyses and metaphyses appeared normal. The involved areas showed a dense thickened cortex encroaching upon the marrow cavity. The skull revealed basilar density while the jaw showed no thickening.

A biopsy was taken from the diaphysis of the right femur. It was noticed that normal bone of metaphysis suddenly changed to a thickened, rough, pebbly surface completely and symmetrically involving the diaphysis of the femur. The periosteum appeared thickened. The cortical bone was dense and offered considerable resistance to chiselling.

Specimen for microscopic examination consisted of a block of bone, bone marrow, and overlying soft tissue. The microscopic sections showed the bony trabeculae to be broad and dense, and the marrow, in places, to be more fibrotic than usual. In some areas, many osteoclasts as well as osteoblasts were present. The soft tissues were not remarkable.

Cultures, which were taken at the time of operation, were later reported as sterile.

DISCUSSION

Engelmann's disease has been fairly well delineated by its typical clinical, roentgenologic, and morphologic manifestations.

The differential diagnosis has been reviewed by several previous authors and includes Paget's disease, osteopetrosis, scurvy, polyostotic fibrous dysplasia, hypervitaminosis A, and infantile cortical hyperostosis.

No light has been shed on the etiology and pathogenesis of the basic disorder, however. The disease, although most dramatically seen in the bone, is not limited to this tissue. The peculiar neurological findings, the disturbances in motor function, and poor nutritional pattern seem to be evidence that this disease is a systemic one.

The age incidence and physical findings do not point in any significant direction in terms of etiology. There have been no reports of fever, leucocytosis or increased sedimentation rate, and bacteriologic studies, when done, have been negative. Laboratory studies, no matter how thorough, have been noninformative.

Roentgen studies have revealed a characteristic pattern of symmetrical involvement of the diaphysis with cortical thickening and constriction of the medullary canal. The epiphysis and metaphysis are not involved.

Additionally, biopsy showed fibrotic marrow and broad, dense, bony trabeculae with areas of increased osteoblasts and osteoclasts. The tissue showed no abnormal cells, indicating further that the bone picture may be a response to some systemic disorder.

A clue to the etiology of Engelmann's disease may lie in the work of J. B. Thiersch[19] of South Australia who obtained similar skeletal lesions experimentally by injecting one-day-old chicks intravenously with human myeloid leukemic material.

Leukemic infiltrations of internal organs were not seen in the experimental birds until the third transmission when typical lymphomatosis occurred. Roentgenographic studies of the birds showed the bony lesions were always bilateral, almost always confined to the diaphysis, leaving the epiphysis and cartilaginous ends unchanged.

In most birds, only the tubular bones were involved, but in a few very advanced cases, the flat bones, including the head and vertebra and breast bones, were also affected. The lesions were predominantly of the endostial and periosteal type: the endostial bone formation caused narrowing of the

marrow cavity by cortical thickening of the central parts of the shafts of the long bone. The findings are very similar to descriptions of roentgen findings seen in Engelmann's disease.

Biopsy of the experimental lesions which developed late consisted primarily of lamellar bone with a fibrous marrow. Again, this description coincides with the biopsy findings in Engelmann's disease.

It may be postulated that Engelmann's disease is but one of a family of sclerotic bone diseases which may merge into each other. Thiersch showed that a great variety of lesions can be obtained because bony changes can be arrested at any stage. This is what may have occurred in a case of unclassified juvenile bone distrophy in a 7-year-old boy whose x-ray appearance is similar to that seen in Engelmann's disease but which involves only the skull and one humerus, radius, and ulna, reported by Geschickter and Copeland.[11]

SUMMARY

1. An additional case of Engelmann's disease has been reported. This is the twelfth of its kind.

2. Clinical examination shows that the disease is systemic, indicated by the presence of muscular weakness and nutritional failure.

3. Roentgen studies reveal that the main lesions of Engelmann's disease are progressive, symmetrical, endostial, and periosteal new-bone formation in the diaphysis of long bones.

4. Microscopically, the lesion is simply that of a solid osteopetrosis.

5. The etiology and pathogenesis of the disease is unknown. The authors believe that the work of Thiersch in developing experimental bone lesions may be of considerable importance in the further investigation of all bone diseases characterized by osteopetrosis.

REFERENCES

1. Engelmann, Guido: Ein Fall von Osteopathia Hyperostotica (Sclerotisans) Multiplex Infantilis, Fortschr. a.d. Geb. d. Röntgestrahlen **39:** 1101, 1929.
2. Riley, C. M., and Shwachman, H.: Unusual Osseous Disease With Neurologic Changes; Report of Two Cases, Am. J. Dis. Child. **66:** 150, 1943.
3. Neuhauser, E. B. D., Shwachman, H., Wittenborg, M. H., and Cohen, J.: Progressive Diaphyseal Dysplasia, Radiology **51:** 11, 1948.
4. Sear, H. R.: Engelmann's Disease, Osteopathia Hyperostotica Sclerotisans Multiplex Infantilis; Report of a Case, Brit. J. Radiol. **21:** 236, 1948.
5. Michaelis, L. S.: Engelmann's Disease, Proc. Roy. Soc. Med. **42:** 271, 1949.
6. Bingold, A. C.: Engelmann's Disease; Osteopathia Hyperostotica (Sclerotisans) Multiplex Infantilis; Progressive Diaphysial Dysplasia, Brit. J. Surg. **37:** 266, 1950.
7. Stronge, R. F., and McDowell, H. B.: A Case of Engelmann's Disease; Progressive Diaphyseal Dysplasia, J. Bone & Joint Surg. **32B:** 38, 1950.
8. Gillespie, J., and Mussey, R.: Progressive Diaphyseal Dysplasia (Engelmann's Disease), J. PEDIAT. **38:** 55, 1951.
9. Gulledge, W. H., and White, J. W.: Engelmann's Disease (Progressive Diaphyseal Hyperostosis), J. Bone & Joint Surg. **33A:** 793, 1951.
10. Thiersch, J. B.: Contribution to the Radiology and Pathology of Transmissible Avian Osteopetrosis-Lymphomatosis, Radiology **51:** 100, 1948.
11. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 3, Philadelphia, 1949, J. B. Lippincott, Co., p. 765, Fig. 626.

OMENTAL SEGMENTAL INFARCTION

A Report of Two Cases in Children

Francis P. Catanzaro, M.D.,* Springfield, Mass., and
John E. Farley, Jr., M.D.,** Providence, R. I.

OMENTAL segmental infarction is a rare surgical condition which simulates many acute abdominal emergencies. It has been reported frequently in adults, usually associated with vascular disease, but apparently is quite uncommon in children, only one case having been reported in twenty years in addition to the case reported by Manfredi.[1] Because there are no constant differential points clinically, the diagnosis is made postoperatively in all cases. The etiology is unknown.

CASE REPORTS

Case 1.—D. C., a 10-year-old white male, was admitted to the Springfield Hospital on July 10, 1951, with a history of abdominal pain of four days' duration. The pain was first noticed in the right upper abdomen and was dull and constant in nature. It settled in the right lower quadrant after several hours. He complained of loss of appetite but had no other presenting symptoms until the morning of hospitalization when he had two episodes of vomiting and stated that the pain was more severe. He was seen by a physician and hospitalization was advised.

The family and past histories were negative.

Physical examination revealed a moderately obese, well-developed young male child lying quietly in bed. The positive findings were confined to the abdomen which was slightly distended, with marked spasm of the right rectus and point tenderness with rebound tenderness, most marked about 2 cm. above MacBurney's point. Rectal examination was negative. The temperature was 100.2° F., pulse 92, and respirations 24.

Examination of the blood disclosed a white cell count of 11,900 with 73 per cent neutrophils. The urine was negative.

A diagnosis of acute appendicitis was made and laparotomy done. The appendix was negative. A 5.5 cm. by 3.5 cm. area of infarcted omentum was found extending from the right lower edge of the omentum overlying the cecal region. The segment of infarcted omentum was excised and incidental appendectomy also carried out. The specimen was grossly described by the pathologist as a segmental omentum infarct. On microscopic examination, venous thrombosis with venous congestion and extravasation of blood were seen.

The patient had an uneventful postoperative course and left the hospital one week after operation.

Case 2.—J. S., a 4-year-old white female, was admitted on March 14, 1950, to the surgical service of St. Joseph's Hospital, Providence, with a one-day history of generalized "soreness and pain" in the abdomen. There had been no vomiting but there was diarrhea of six hours' duration. The night prior to admission, the child "could not straighten up" because of the pain. On the morning of admission, she pointed to the right lower quadrant when asked where the pain was. There was no history of trauma.

The remainder of the history was noncontributory.

Physical examination revealed a moderately obese, white, well-developed female child in no acute distress but

*Resident in Surgery, Springfield Hospital.
**Resident in Pediatrics, Charles V. Chapin Hospital.

complaining of pain in the right lower quadrant. The pulse was 80, and the temperature 100° F., rectally. The positive findings were limited to the abdomen. There was slight distention evident in the right lower quadrant with direct and rebound tenderness and moderate, apparently involuntary, resistance to palpation. A rectal examination was equivocal.

White blood count and differential on admission was 11,350 with 55 polymorphonuclears, 43 lymphocytes, and 2 monocytes. Admission urinalysis showed a cloudy, acid urine with a specific gravity of 1.024, albumin 1 plus, sugar O, sediment—few squamous epithelial cells, 12 leukocytes per high-power field (noncatheterized). Repeat urinalysis the day after admision was essentially negative.

The patient was seen by two members of the surgical staff and the pediatrician, and the decision was made to perform a laparotomy with a presumptive diagnosis of acute appendicitis. A right rectus incision was made, and when the peritoneum was opened, it was seen that the appendix appeared normal but that adherent to the cecum was an omental mass at the right lower margin, approximately 9 cm. by 4 cm. and flattened, well outlined, and with normal omentum surrounding, firm and purplish black in color. There was no other apparent pathology in the abdominal cavity. The mass was removed for biopsy along with a pea-sized piece of "meatlike" tissue also found in the omentum. The appendix was removed and the abdomen was closed in the usual manner. Microscopically, the appendix was not acutely inflamed but the omental tissues were engorged and stroma infiltrated with lymphocytes, plasma cells, and red blood cells consistent with omental segmental infarction.

The patient's postoperative hospital course was uneventful and the patient was discharged on the tenth hospital day.

DISCUSSION

There have been many etiological theories advanced to explain this unusual condition. Pines and Rabinovitch[2] in 1940 and Totten[3] in 1942 advocated the "pull mechanism" theory. They noted that as a result of the close communication existing between the blood supply of the stomach and omentum, a strain was placed on the thin-walled veins of the omentum by vascular congestion following a meal. During this time, any additional stress from increased intra-abdominal tension incident to straining, coughing, sneezing, lifting, or direct trauma to the abdomen may be sufficient to cause primary rupture of the dependent veins of the omentum, with hemorrhage and secondary thrombosis. Eger and Barto[4] in 1949 suggested that the almost constant location of the infarct along the right lower edge of the omentum may indicate that some anatomic peculiarity of the venous drainage in that region may predispose to thrombus formation. As previously stated, we have observed that in our cases both children were moderately obese with a well-developed, fatty omentum. Whether this situation is a predisposing factor or only incidental remains open to conjecture. In neither of our cases was trauma a factor so far as is known.

The clinical and laboratory findings closely simulate acute appendicitis. Occasionally the syndrome can be mistaken for other causes of the acute abdomen but in all instances previously reported, in adults and children, the situation was severe enough to warrant exploration. It is our belief that the diagnosis of segmented omental infarction cannot be made until exploratory laparotomy is performed. One point might suggest the diagnosis preoperatively. The abdomen is characterized by generalized tenderness over the site of pain with a more localized area of exquisite tenderness as in our case D. C. This finding was a marked feature in most cases, adults and children, reported to date.

The treatment is excision of the segment of infarcted omentum and uncomplicated convalescence generally ensues.

Besides being a surgical rarity, perhaps the only importance of this entity is the speculation that since it occurs in adults with vascular disease, it may be that the occurrence of omental segmental infarction in childhood is a suggestion of candidacy for future vascular disturbance. At present this is merely speculation and the notation in each of our two cases of moderate obesity, probably coincidental.

SUMMARY

Two cases of an extremely rare surgical lesion in children have been presented with a brief review of the literature, citing plausible theories as to the mechanism of etiology in idiopathic segmental omental infarction.

REFERENCES

1. Manfredi, D. H.: Omental Segmental Infarction in Infancy, Arch. Pediat. **67**: 247, 1950.
2. Pines, B., and Rabinovitch, J.: Idiopathic Segmental Infarction of Greater Omentum, Surg., Gynec. & Obst. **71**: 80, 1940.
3. Totten, H. P.: Primary Idiopathic Segmental Infarction of Greater Omentum, Am. J. Surg. **56**: 676, 1942.
4. Eger, S. A., and Barto, R. E., Jr.: Primary Idiopathic Segmental Infarction of Greater Omentum, Am. J. Surg. **78**: 518, 1949.

Medical Progress

FACTORS OF IMPORTANCE IN BREAST MILK

THERESA B. HADDY, M.D., AND FORREST H. ADAMS, M.D.
MINNEAPOLIS, MINN.

BREAST milk has always been considered the natural food for babies. Just as the milk of other mammals is specific for their young, human milk is specific for human infants. In recent years the emphasis has been largely on the psychological aspects of breast feeding. The warm, close communion between mother and baby in the nursing process has been stressed. This is surely appropriate. On the other hand, the physiological importance of breast milk has not been neglected. Much new and interesting information has been published recently about the composition of human milk. It appears, therefore, that there is need at this time for a review of the constituents of breast milk which make it valuable as an ideal food for human babies.

Physicians in general feel that breast feeding is on the decline. This is no doubt a true impression. Several recent studies give accurate information as to the present incidence of breast feeding in this country and in parts of Great Britain. They tend to confirm the existence of a downward trend of breast feeding in the United States. In England the incidence of early breast feeding has not changed since the prewar years, but mothers appear to be weaning their babies earlier.

Two-thirds of all hospitals in the United States were recently surveyed by Bain.[1] She found that in 1946 and 1947 two-thirds of all babies in the nation were on breast or mixed feedings at the time of discharge from the hospital and one-third were on bottle feedings. The statistics varied markedly in different regions. In the Southeast and Southwest 82 per cent of babies were breast fed, while in the Northeast 61 per cent were bottle fed. More infants were breast fed in rural than in urban areas, and more in small and large hospitals than in medium-sized hospitals. The incidence of breast feeding was higher among babies who were discharged under eight days of age than among those who were hospitalized longer. This suggests that a number of babies are weaned shortly after coming home from the hospital. No follow-up study was done to confirm this impression. Bain's survey may be compared with a study of mothers in 1916 at the Children's Hospital in Philadelphia.[2] During a fifteen-year period 80 per cent of women breast fed their babies in the neonatal period and 42 per cent nursed six months or longer.

From the Department of Pediatrics, University of Minnesota, and the Minneapolis General Hospital.

In England, during the postwar years, 1946 and 1947, Dummer[3] found that there was an inclination toward early weaning. The incidence of breast feeding in the neonatal period, however, was approximately the same as in the prewar years. In an area of North Hertfordshire 84 per cent of infants were on complete, and 5.5 per cent on partial, breast feedings during the neonatal period. Only 13.2 per cent of infants were on complete breast feedings at six months of age. This contrasted with studies in Liverpool during 1937 in which 29 per cent of babies were still being breast fed,[4] in Brewis, Newcastle, during 1938 in which 34.7 per cent of babies were still on breast feedings,[5] and in Newbiggin during 1942 in which 19 per cent of babies were still being nursed at 6 months of age.[6] The incidence of breast feeding in the neonatal period in these prewar investigations ranged from 87 to 67 per cent.

COLOSTRUM

Human colostrum is the milk which is secreted during the last few months of pregnancy and the first two to five days after parturition. It is yellow in color and much thicker than established milk. It has a specific gravity of 1.050 to 1.060. Colostrum contains only one-half as much sugar and fat, five or six times as much protein, and twice as much mineral salts as mature milk. It contains globulin, in contrast to later milk, and therefore coagulates on boiling. It is very rich in sodium and phosphorus. On microscopic examination, colostrum contains leukocytes, epithelial cells, fat globules, and colostrum corpuscles. These are thought to be fat-laden neutrophils which remove the fat whenever milk stasis occurs. Colostrum appears to have some laxative action in the excretion of meconium stools. It has been considered important in the development of immunity in the infant. The existence of such a mechanism has not been conclusively established, but large numbers of antibodies are presumably present in the globulin fraction.

BREAST MILK

Human breast milk is warm, fresh, and free from pathogenic bacteria. It is bluish-white in color. It has a specific gravity of 1.030 and a calorie value of 20 calories per ounce. It is amphoteric or alkaline in reaction. Breast milk contains the essential food elements in the following average proportions: fat 4 per cent, protein 1.25 per cent, lactose 7 per cent, minerals 0.25 per cent, and water 87.5 per cent. The fat content varies widely from 2 to 8 and even up to 10 per cent. The fat consists chiefly of the neutral fats, tripalmitin, tristearin, and triolein, with triolein making up about one-half. The protein content is fairly constant although it may vary from 1 to 1.5 per cent. It is made up of about 40 per cent casein and 60 per cent lactalbumin. The lactalbumin portion is more important. It is not better utilized[7] as was previously thought, but it more nearly approaches the composition of the body proteins and is richer in the essential amino acids. The sugar of breast milk, lactose, appears to be identical with that of other mammals. It is constant in amount and does not vary from 7 per cent. The mineral salts are small in amount but readily absorbed and utilized. The vitamins are usually present in adequate amounts if the mother's diet is adequate.

The composition of breast milk secreted by different women varies widely. It may be generally assumed that all constituents are present in normal amounts if the mother's diet is well balanced and her emotional and physical health good. Variations in quality occur, however, during a single nursing.[8] The percentage of fat, and of protein to a lesser degree, tends to increase toward the end of a nursing period. Variations in quality also occur according to the "maturity" of the milk.[9] The protein and mineral fractions gradually decrease as time after parturition elapses, and the sugar and fat portions gradually increase. During the period of change it is called "transition milk." Its composition becomes stable at about the end of the first month and from then on the "mature milk" shows little variation in composition.

TABLE I. APPROXIMATE QUANTITIES OF BREAST MILK OBTAINED BY HEALTHY INFANTS

AGE	PER NURSING (C.C.)	PER DAY (C.C.)
1 wk.	60	300
2 wk.	90	540
3 wk.	105	600
4 wk.	120	660
2 mo.	135	720
4 mo.	150-180	660-810
6 mo.	150-210	750-960

Demand is the most important single factor that determines the amount of breast milk obtained from the average nursing mother. The quantity taken is directly proportional, within limits, to the weight of the infant and to his interest in food.[10] Table I illustrates the changes in quantity of milk produced as the supply adjusts to the infant's growing needs.

COMPARISON WITH COW'S MILK

No discussion of human milk is complete unless a comparison with cow's milk is included. This information is given briefly in Tables II, III, and IV. The amount of water is the same in both milks. There is a larger proportion of protein in cow's milk. A greater percentage of lactalbumin is present in human milk, however, so that the actual amount of lactalbumin in human milk is larger. For reasons previously discussed, lactalbumin is perhaps a better food for human babies. The larger milk curd produced by cow's milk is chiefly due to the larger amount of casein, which is coagulated by acid or rennin. The proportion of fat is the same in both milks. The fat of cow's milk contains a fairly high percentage of fatty acids. The fat of human milk, however, is almost entirely made up of neutral fats which become enmeshed in the soft, flocculent breast milk curds and are readily assimilated by the human baby. Although the sugar of both milks, lactose, is the same, human milk contains more.

TABLE II. COMPARISON OF THE CHIEF CONSTITUENTS OF HUMAN MILK AND COW'S MILK

	HUMAN MILK (PER CENT)	COW'S MILK (PER CENT)
Water	87.5	87.5
Protein	1.25	3.25
Lactalbumin	0.8	0.4
Casein	0.4	2.8
Fat	4.0	4.0
Sugar (Lactose)	7.0	4.5

Cow's milk contains greater proportions of all of the mineral salts except iron and copper. Both of these minerals, which are important in the production of hemoglobin, are present in larger amounts in human milk. Hu-

man milk, except in maternal deficiency, also contains more iodine. Large quantities of certain minerals are apparently not beneficial to the human baby. It has been shown that hypocalcemic tetany of the newborn does not occur in breast-fed infants because human milk contains a smaller phosphorus to calcium ratio of approximately 1:2, in contrast to cow's milk which contains almost equal amounts of phosphorus and calcium.

TABLE III. COMPARISON OF THE MINERAL CONTENT OF HUMAN MILK AND COW'S MILK*

	HUMAN MILK (PER CENT)	COW'S MILK (PER CENT)
Total ash	0.20	0.75
Calcium	0.034	0.122
Magnesium	0.005	0.013
Potassium	0.048	0.154
Sodium	0.011	0.06
Phosphorus	0.015	0.09
Sulfur	0.0036	0.031
Chlorine	0.036	0.116
Iron	0.0001	0.00004
Copper	0.00003	0.00002

*Jeans, P. C.: The Feeding of Healthy Infants and Children, J. A. M. A. 120: 913-921, 1942.

Human milk has higher concentrations of vitamins A, D, C, E, and inositol than does cow's milk. Moreover, vitamins C, E, K, thiamin, and riboflavin are altered by the handling which cow's milk undergoes. The vitamins will be discussed individually.

VITAMINS

Vitamin A.—The average concentration of vitamin A in mature human milk is 61 μg (263 U.S.P. units) per 100 c.c.[11] Of the total carotenoid content, 30 to 40 per cent is carotene. Vitamin A is high immediately after parturition, decreasing gradually to the average on the tenth day and remaining level from then on throughout the period of lactation. The vitamin A concentration remains normal if the maternal diet is adequate, becoming low only when the mother's nutrition is deficient. The average concentration of vitamin A in cow's milk is 33 μg (182 U.S.P. units) per 100 c.c.[12] This is almost entirely beta carotene. The vitamin A content of cow's milk is quite stable.

Vitamin D.—Human milk contains 0.4 to 10 U.S.P. units of vitamin D per 100 c.c. Exposing the mother to sunlight or supplementing her diet can increase the vitamin D concentration in breast milk to some extent. Neither human milk nor cow's milk, however, can be relied upon to prevent rickets in the infant. Cow's milk contains 2 to 4 U.S.P. units of vitamin D per 100 c.c.[12] This amount is decreased during the winter months. It may be considerably increased by irradiation of the milk with ultraviolet rays. There is no appreciable loss of vitamin D by commercial handling.

Antirachitic Factor.—An antirachitic factor, which has been demonstrated in cow's milk, is not present in human milk.[13, 14] Rickets can be prevented in rats when 20 to 25 c.c. of cow's milk are added daily to a rachitogenic diet, and can be cured when 30 c.c. are added to the diet. Human milk, on the other hand, induces no healing when amounts up to 40 c.c. are added daily to rats' diets.

Vitamin C.—The average vitamin C level for mature human milk is 5 mg. per 100 c.c.[15] Colostrum contains a slightly larger amount, 7 mg. per 100 c.c. The ascorbic acid level remains constant in mature milk, being more closely correlated to the volume of milk than to maternal intake.[16] The average value for bovine milk is 2 mg. per

100 c.c.[12] Cow's milk is likely to suffer great losses in vitamin C content during the processing and delivery.

Thiamin.—The average total thiamin content of mature milk is 14.4 μg per 100 c.c.[17] About 30 per cent of this is free thiamin. During the first few post-partum days, very little thiamin is present in human milk. It increases gradually during the first few weeks of lactation. The mother's diet is the chief determinant of amount, but her emotional state and physical health are also important. The average value of thiamin for cow's milk is 38 μg per 100 c.c.[12] This vitamin is unstable to heat, and losses occur during pasteurization.

Riboflavin.—Mature human milk contains an average of 38.4 μg of riboflavin per 100 c.c.[18] Free riboflavin makes up 43 to 86 per cent of the total riboflavin. The concentration rises rapidly at first and levels off on the tenth post-partum day. It seems to be definitely dependent on maternal intake. Cow's milk contains about 200 μg per 100 c.c.[12] Riboflavin is stable to all phases of handling except exposure to light. Because of this, large losses are likely to occur during the marketing process.

Nicotinic Acid.—The average nicotinic acid content of mature human milk is 186 μg per 100 c.c.[19] It decreases slightly for 2 to 4 days after parturition, rises rapidly to 245 μg per 100 c.c. on the tenth day, and then decreases gradually. The secretion of nicotinic acid varies directly with the volume of milk and has no relation to intake. Cow's milk contains 85 μg per 100 c.c.[12] This vitamin is stable in cow's milk.[20]

Pantothenic Acid.—The mean value of pantothenic acid for mature human milk is 249 μg per 100 c.c.[19] It increases rapidly for the first five days of lactation and slowly for the next five days. There appears to be some variation according to diet. The average amount of pantothenic acid in cow's milk is 350 μg per 100 c.c.[12] This vitamin is not decreased in value during commercial handling.[20]

Biotin.—Mature human milk contains an average of 0.81 μg of biotin per 100 c.c.[19] It remains at a very low level for the first five post-partum days, increases slowly to about one-half the normal by the tenth day, and thereafter continues to increase slowly until it reaches the normal. There appears to be some correlation with intake. The mean value for cow's milk is 3 μg per 100 c.c.[12] Biotin is stable in cow's milk.[20]

Pyridoxine.—There are 4 μg of pyridoxine per 100 c.c. of mature human milk.[21] The pyridoxine content of cow's milk is 67 μg per 100 c.c.[22] No significant loss of this vitamin occurs during the commercial preparation of cow's milk.

Inositol.—Mature human milk contains 33 mg. of inositol per 100 c.c., and cow's milk contains 18 mg. per 100 c.c.[21]

Folic Acid.—The average value of folic acid for mature human milk is 0.3 μg per 100 c.c., and the average value for pasteurized bovine milk is approximately 0.4 μg per 100 c.c.[23]

Vitamin B_{12}.—Human milk contains 0.2 μg of vitamin B_{12} per 100 c.c., and cow's milk contains 0.4 μg per 100 c.c.[24]

Vitamin E.—Mature human milk contains an average of 0.14 mg. of vitamin E per 100 c.c.[25] Colostrum, however, has a very high content of vitamin E, up to 3.6 mg. per 100 c.c., which

decreases very gradually to normal during the period of lactation. A recent study by Wright[26] indicates that mammary transfer of vitamin E is excellent although placental transfer is poor. The serum tocopherol levels of pregnant women have been known to rise to almost twice the normal. The newborn infants in Wright's study, however, had levels at birth which were approximately one-fifth of their mothers'. On the fourth post-partum day the serum tocopherol levels of the nursing mothers had fallen much lower than those of the non-nursing mothers. By the sixth post-partum day the serum tocopherol levels of the breast-fed babies had increased much more rapidly than those of the non-breast-fed babies. These differences with regard to the infants were still evident up to 8 months of age. Cow's milk contains an average of 0.12 mg. per 100 c.c.[27] This value is slightly decreased during the handling process.

Vitamin K.—Mature breast milk averages 50 Dam-Glavind units, about 3 to 5 μg, of vitamin K per 100 c.c.[28] This amount is adequate for the human baby. Sells[29] showed the vitamin K requirement of a newborn infant to be very low, about 1 μg per day. He pointed out that hemorrhagic disease due to hypoprothrombinemia of the newborn can be prevented by breast feeding. Cow's milk contains an average of 200 Dam-Glavind units, about 13 to 20 μg, of vitamin K per 100 c.c.[28] This is destroyed when the milk is pasteurized or evaporated but not when it is powdered.

Table IV. Comparison of the Vitamin Content of Human Milk and Cow's Milk

	Human milk per 100 c.c.	Cow's milk per 100 c.c.
Vitamin A	61 μg (263 U.S.P. units)	33 μg (182 U.S.P. units)
Vitamin D	0.4-10 U.S.P. units	2-4 U.S.P. units
Vitamin C	5 mg	2 mg.
Thiamin	14.4 μg	38 μg
Riboflavin	38.4 μg	200 μg
Nicotinic acid	186 μg	85 μg
Pantothenic acid	249 μg	350 μg
Biotin	0.81 μg	3.0 μg
Pyridoxine	4.0 μg	67 μg
Inositol	33 mg.	18 mg.
Folic acid	0.3 μg	0.4 μg
Vitamin B_{12}	0.2 μg.	0.4 μg
Vitamin E	0.14 mg.	0.12 mg.
Vitamin K	4 μg	16 μg

ANTIBODIES

Most of the work on the passive transfer of immune bodies through human milk has been done in past years. Little to confirm it has been done in recent years. Two substances appearing in human milk are of practical interest at the present time. Rh antibodies have been shown to appear in the milk of mothers with high anti-Rh serum titers. The question as to whether or not these mothers should breast feed has been answered in the affirmative. An antipoliomyelitic material has been reported to occur in human milk. Proof of the presence of such a protective substance would re-emphasize the importance of breast milk for human babies.

Rh Antibody.—The appearance of Rh agglutinins in human breast milk was first observed in 1942 by Witebsky.[30] It was confirmed in 1944 by Fisk.[31] This author demonstrated that an Rh antibody in the milk was identical with that present in the maternal blood stream. Shortly thereafter cases were reported[32, 33] of babies with erythroblastosis who remained anemic while they were on breast feedings. The infants apparently improved after weaning. It was thought, accordingly, that milk from an Rh-negative mother might be detrimental to her Rh-positive baby. In 1947 Cathie[34] disproved this impression. His study revealed that although Rh antibodies are not readily destroyed in infants' stomachs, they are not demonstrably absorbed into their blood streams. The fasting gastric contents from twenty babies, when mixed with high Rh-antibody titer serum and incubated for one hour, caused no fall in titer of the serum. An Rh-positive adult volunteer suffered no ill effects from drinking 15 ounces of high titer serum. Twelve Rh-positive babies with inoperable conditions such as spina bifida had no demonstrable antibodies in their blood serums after being fed high titer serum for one day. One erythroblastotic baby was fed high titer serum for two days after his Coombs' test had become negative; his Coombs' test continued to be negative. Another erythroblastotic baby was fed breast milk with an anti-Rh titer of 32 after his Coombs' test had become negative; no Rh antibodies were demonstrated in his serum. Cathie was able to conclude that the weaning of infants with hemolytic disease because of antibodies in their mothers' milk is not justified.

Antipoliomyelitic Substance.—Sabin[35] recently reported an antiviral substance which is apparently present in human milk. He found that breast milk and blood serum from thirty mothers could neutralize the Lansing strain of poliomyelitis virus when tested by intracerebral inoculation into mice. Milk which protected against the Lansing virus did not always protect against the Japanese B virus. Because the titers of antibody in the serum and of antipoliomyelitic substance in the milk did not correlate, and because the substance was resistant to heat, the antipoliomyelitic material was thought not to be antibody. All early breast milk specimens showed activity, and 80 per cent of milk samples obtained three to ten months after delivery still contained antipoliomyelitic substance. Milk obtained from only 22 per cent of nine cows, on the other hand, protected against poliomyelitis. Since the probable portal of entry of the poliomyelitis virus is the gastrointestinal tract, Sabin has suggested that breast feeding beyond the third month might be of value in preventing or modifying the disease.

DRUGS AND TOXINS

The question of drug excretion through breast milk has always been one of controversy. Many infants are weaned because there is fear of transmission of some drug which is being administered to the mother. Probably in most cases this is not justified. There seems to be a general feeling that lactating women should avoid alcohol and nicotine. Certainly in most cases this is not justified.

Alcohol.—Chronic alcoholic mothers seldom nurse their babies. Even

though large quantities of alcohol may be consumed, the milk will contain only small quantities of alcohol. The maximum amount is generally considered to be too small to be harmful to an infant. One case of acute toxicity with deep coma has been reported[36] in a breast-fed baby whose mother had ingested a large quantity of wine.

Nicotine.—A well-controlled study of fifty-five cigaret-smoking mothers by Perlman[37] showed small amounts of nicotine to be present in the breast milk of each one in direct correlation with the number of cigarets used. Lactation was not significantly decreased, and the nurslings were in no way adversely affected. Most workers agree with these findings. It has been postulated that the infants develop tolerance to the drug, especially since the mothers have usually smoked during the antenatal period. One case of toxicity in a breast-fed infant 6 weeks of age has been reported.[36] The symptoms, which were restlessness, insomnia, tachycardia, circulatory disturbances, vomiting, and diarrhea, disappeared when the infant was weaned.

Caffeine.—This drug is transmitted through breast milk in traces up to 1 per cent.[38] No toxicity due to caffeine has been observed in breast-fed infants whose mothers drank coffee or tea.

Barbiturates.—Barbiturates, as studied by Tyson,[39] are transmitted through breast milk, especially when administered in single large doses. Sedative ½ grain doses of phenobarbital produced detectable amounts in the breast milk of 90 per cent of forty-one mothers. Hypnotic 1½ grain doses of phenobarbital produced detectable amounts in 100 per cent of the cases. Only two of the forty-one infants showed clinical effects of sedation. Both were cases in which the mothers had received single 1½ grain doses.

Opiates.—Neither morphine nor codeine are significantly transmitted through breast milk. Even the milk of a morphine addict taking up to 20 grains daily did not show traces of the drug.[40]

Demerol.—No traces of Demerol have been found in the milk of mothers taking regular doses of Demerol.

Salicylates.—Salicylates are consistently excreted through breast milk, even when the nursing mother takes as small a dose as 10 grains.[41] The amount is small, however, and no toxic effects to an infant have been observed.

Halogens.—Bromides are transmitted through breast milk in significant amounts. Toxicity to the infants includes sedation and papulopustular eruptions.[42] Iodine and fluorine are transmitted in only minimal amounts.

Quinine.—Only slight traces of quinine are found in breast milk even when a mother is taking large doses. The amount is too small to be toxic to an infant.

Ergot.—Ergot has been found in breast milk and some infants have been reported to show toxic effects.

Hyoscine and Atropine.—These drugs appear in breast milk in only very slight traces if at all. Diminution of the milk supply may occur, but this is questionable.

Laxatives.—Of the laxatives, cascara is the only one which is transmitted through breast milk. It produces diarrhea in the babies.[43] Phenolphthalein is not transmitted through breast milk in detectable amounts.[41]

Heavy Metals.—Lead, mercury, and arsenic are definitely excreted in breast milk and can be toxic to infants. Cases of lead encephalitis in infants have been reported.[44] Lead nipple shields were used by one mother, and lead was excreted in the breast milk for at least several weeks after the nipple shields were no longer used.

Therapeutics.—Sulfonamides are transmitted through breast milk in small amounts. These amounts usually are not large enough to cause toxic effects to the infant unless he has an idiosynerasy. Penicillin is transmitted through breast milk in small amounts in about 70 per cent of the cases. These, again, are not large enough to cause toxic effects to the infant, unless he has been sensitized.

MILK FACTOR OF BREAST CANCER

A virus milk factor has been shown to produce breast carcinoma in mice. During the past few years small, spherical particles with diameters ranging from 20 to 200 mμ have been observed in nursing mice known to carry the mammary cancer agent. Similar particles have been seen in tumor cells or tumor cell extracts. A number of investigators believe that these particles actually represent the carcinoma virus.

The recommendation, based on these observations on mice, has been made that women with family histories of breast carcinoma should not nurse their children.[45] It has been pointed out, on the other hand, that there has been no proof of such a factor existing in human beings, and that such a restriction would be impractical. Since most breast carcinomas appear around middle age, many women will have had all of their children and nursed them through infancy before their own mothers have demonstrable breast carcinomas.[46]

The milk of nursing mothers has been recently studied by Gross.[47] The milk of ten women whose close relatives had known breast carcinoma contained spherical particles which were similar to those thought to be the mouse carcinoma agent. The milk of thirty-two women whose family histories were free of breast carcinoma contained few or no such particles. Gross was unable to draw any definite conclusions from this work. He did, however, suggest that the milk factor of mammary carcinoma deserves further study in human beings.

SUMMARY

A review of the recent literature in regard to the composition of breast milk has been presented. The chief constituents, minerals, vitamins, antibodies, and the breast cancer milk factor, have been discussed. The mammary transfer of various drugs and toxins has been reviewed. From this it appears that a number of drugs are to be avoided by nursing mothers. It would be well to limit phenobarbital administration to sedative ½ grain doses rather than hypnotic 1½ grain doses. Bromides should be avoided. If a laxative is indicated, it would be advisable to select one other than cascara. The heavy metals, lead, mercury, and arsenic, should be avoided by a nursing mother.

REFERENCES

1. Bain, K.: The Incidence of Breast Feeding in Hospitals in the United States, Pediatrics **2**: 313, 1948.
2. Mitchell, A. G.: The Duration of the Nursing Period in Women of the United States, J. A. M. A. **66**: 1690, 1916

3. Dummer, F. H. M.: A Study of the Post-War Incidence of Breast Feeding, Brit. M. J. **2**: 14, 1949.

4. Robinson, M.: A Review of Twenty Years of Breast Feeding in Liverpool, Arch. Dis. Child. **14**: 259, 1939.

5. Spence, J. C.: The Modern Decline of Breast-Feeding, Brit. M. J. **2**: 729, 1938.

6. Hughes, E. L.: The Incidence of Breast-Feeding in a Small Mining Town, Brit. M. J. **2**: 69, 1942.

7. Mueller, A. J., and Cox, W. M., Jr.: Comparative Nutritive Value of Casein and Lactalbumin for Man, Science **105**: 580, 1947.

8. Macy, I. G., Nims, B., Brown, M., and Hunscher, H. A.: Human Milk Studies: VII. Chemical Analysis of Milk Representative of the Entire First and Last Halves of the Nursing Period, Am. J. Dis. Child. **42**: 569, 1931.

9. Nims, B., Macy, I. G., Hunscher, H. A., and Brown, M.: Human Milk Studies: X. Daily and Monthly Variations in Milk Components as Observed in Two Successive Lactation Periods, Am. J. Dis. Child. **43**: 1062, 1932.

10. Smith, C. H., and Merritt, K. K.: The Rate of Secretion of Breast Milk, Am. J. Dis. Child. **24**: 413, 1922.

11. Lesher, M., Brady, J. K., Williams, H. H., and Macy, I. G.: Human Milk Studies: XXVI. Vitamin A and Carotenoid Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**: 182, 1945.

12. Lawrence, J. M., Herrington, B. L., and Maynard, L. A.: Human Milk Studies: XXVII. Comparative Values of Bovine and Human Milks in Infant Feeding, Am. J. Dis. Child. **70**: 193, 1945.

13. Hess, A. F., and Weinstock, M.: A Study of the Antirachitic Factor in Human and in Cow's Milk, Am. J. Dis. Child. **34**: 845, 1927.

14. Outhouse, J., Macy, I. G., and Brekke, V.: Human Milk Studies: V. A Quantitative Comparison of the Antirachitic Factor in Human Milk and Cow's Milk, J. Biol. Chem. **78**: 129, 1928.

15. Munks, B., Robinson, A., Williams, H. H., and Macy, I. G.: Human Milk Studies: XXV. Ascorbic Acid and Dehydroascorbic Acid in Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**: 176, 1945.

16. Pratt, J. P., Munks, B., and Macy, I. G.: Metabolism of Women During the Reproductive Cycle: XII. The Effect of Multi-Vitamin Supplements on the Vitamin C Utilization of Nursing Mothers, J. Nutrition **33**: 621, 1947.

17. Roderuck, C. E., Williams, H. H., and Macy, I. G.: Human Milk Studies: XXIII. Free and Total Thiamine Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**: 162, 1945.

18. Roderuck, C. E., Coryell, M. N., Williams, H. H., and Macy, I. G.: Human Milk Studies. XXIV. Free and Total Riboflavin Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**: 171, 1945.

19. Coryell, M. N., Harris, M. E., Miller, S., Williams, H. H., and Macy, I. G.: Human Milk Studies: XXII. Nicotinic Acid, Pantothenic Acid, and Biotin Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**: 150, 1945.

20. Hodnon, A. Z.: The Nicotinic Acid, Pantothenic Acid, Choline and Biotin Content of Fresh, Irradiated, Evaporated and Dry Milk, J. Nutrition **29**: 137, 1945.

21. Williams, R. J., Cheldelin, V. H., and Mitchell, H. K.: Studies on the Vitamin Content of Tissues: II. The B Vitamin Content of Milk From Animals, Pub. 4237, University of Texas, p. 97, 1942.

22. Hodson, A. Z.: The Pyridoxine Content of Fresh, Pasteurized, Evaporated and Dried Milk, J. Nutrition **27**: 415, 1944.

23. May, C. D., Nelson, E. N., Lowe, C. U., and Salmon, R. J.: Pathogenesis of Megaloblastic Anema in Infancy, Am. J. Dis. Child. **80**: 191, 1950.

24. Personal communication from Dr. Charles D. May.

25. Quaife, M. L.: Tocopherols (Vitamin E) in Milk: Their Chemical Determination and Occurrence in Human Milk, J. Biol. Chem. **169**: 513, 1947.

26. Wright, S. W., Filer, L. J., and Mason, K. E.: Vitamin E Blood Levels in Premature and Full Term Infants, Pediatrics **7**: 386, 1951.

27. Hickman, K. C. D.: Vitamin E in Medicine, Record of Chemical Progress **9**: 104, 1948.

28. Dam, H., Glavind, J., Larsen, E. H., and Plum, P.: Investigations Into the Cause of the Physiological Hypoprothrombinemia in New-Born Children: IV. The Vitamin K Content of Woman's Milk and Cow's Milk, Acta med. scandinav. **112**: 210, 1942.

29. Sells, R. L., Walker, S. A., and Owen, C. A.: Vitamin K Requirement of the Newborn Infant, Proc. Soc. Exper. Biol. & Med. **47**: 441, 1941.

30. Witebsky, E., Anderson, G. W., and Heide, A.: Demonstration of Rh Antibody in Breast Milk, Proc. Soc. Exper. Biol. & Med. **49**: 179, 1942.

31. Fisk, R. T., and Foord, A. G.: Further Observations on the Rh Agglutinogen: Studies on an Anti-Rh Serum of Unusual Specificity and the Occurrence of the Same Agglutinin in Breast Milk, Am. J. Clin. Path. **14**: 431, 1944.

32. Cappell, D. F.: The Blood Group Rh: II. Clinical Applications in Transfusion Therapy and in Haemolytic Disease of the Newborn, Brit. M. J. **2**: 641, 1946.

33. Davies, R.: Persistent Anaemia in a Breast-Fed Infant With Erythroblastosis Foetalis, Brit. M. J. **1**: 138, 1947.
34. Cathie, I. A. B.: Breast Feeding in Erythroblastosis Foetalis, Brit. M. J. **2**: 650, 1947.
35. Sabin, A. B.: Antipoliomyelitic Substance in Milk of Human Beings and Certain Cows, Am. J. Dis. Child. **80**: 866, 1950.
36. Bisdom, C. J. W.: Alcohol and Nicotine Poisoning in Nurslings, Maandschr. kindergeneesk. **6**: 299-342, 1937. (Abstr. J. A. M. A. **109**: 178, 1937.)
37. Perlman, H. H., and Dannenberg, A. M.: The Excretion of Nicotine in Breast Milk and Urine From Cigaret Smoking, J. A. M. A. **120**: 1003, 1942.
38. Sapeika, N.: The Excretion of Drugs in Human Milk—A Review, J. Obst. & Gynaec. Brit. Emp. **54**: 426, 1947.
39. Tyson, R. M., Shrader, E. A., and Perlman, H. H.: Drugs Transmitted Through Breast Milk: II. Barbiturates, J. PEDIAT. **13**: 86, 1938.
40. Terwilliger, W. G., and Hatcher, R. A.: The Elimination of Morphine and Quinine in Human Milk, Surg., Gynec. & Obst. **58**: 823, 1934.
41. Kwit, N. T., and Hatcher, R. A.: Excretion of Drugs in Milk, Am. J. Dis. Child. **49**: 900, 1935.
42. Tyson, R. M., Shrader, E. A., and Perlman, H. H.: Drugs Transmitted Through Breast Milk: III. Bromides, J. PEDIAT. **13**: 91, 1938.
43. Tyson, R. M., Shrader, E. A., and Perlman, H. H.: Drugs Transmitted Through Breast Milk: I. Laxatives, J. PEDIAT. **11**: 824, 1937.
44. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, New York, 1940, D. Appleton-Century Co., Inc., p. 183.
45. Hammett, F. S.: Cancer Research and Benefit to Patients, Science **103**: 714, 1946.
46. Macklin, M. T.: Human Breast Cancer and the Milk Factor, Science **104**: 168, 1946.
47. Gross, L., Gessler, A. E., and McCarty, K. S.: Electron-Microscopic Examination of Human Milk Particularly From Women Having Family Record of Breast Cancer, Proc. Soc. Exper. Biol. & Med. **75**: 270, 1950.

Psychologic Aspects of Pediatrics

SIBLING RELATIONSHIPS WITH SPECIAL REFERENCE TO THE PROBLEMS OF THE SECOND BORN

ALFRED E. FISCHER, M.D.
NEW YORK, N. Y.

PEDIATRICIANS and psychologists are increasingly concerned with sibling relationships. Emphasis in the literature has been placed principally on the cautious handling of the first born.[1 a, b] Parents, influenced by newspaper articles, radio talks, lectures and the findings of social scientists, have become more and more apprehensive of the effect of a second child in the family upon the personality development of the older one. However, the harmful results of this attitude on the second child have been inadequately studied. Accordingly, it is the purpose of this paper to inquire into the parents' preoccupation with the first child and to investigate the results of this preferential treatment upon the second born.

The relation of birth order to personality development has been discussed by numerous authors.[2, 3, 4, 5] All agree that ordinal position by itself is only one factor in the behavior pattern. Nevertheless, as will be shown in the present study, when there was close observation of sibling behavior in a given age period, problems in the second born appeared with great regularity. Symptoms of disturbance were manifested most often when the second born was of the same sex as the first and the children were close in age. It was not possible to evaluate statistically the ratio of disturbed to undisturbed second siblings nor to disturbed first or to only children.

From the Department of Pediatrics, Mount Sinai Hospital.

CASE MATERIAL

Thirty-one families, seen during the past six years, were selected for study. They were chosen because behavior on the part of the second born suggested difficulties. Data were obtained primarily from observation of the siblings' behavior in the presence of the pediatrician and secondarily from careful questioning of the mother. All were private patients, thereby permitting the intimate and consecutive observation necessary for this study. The group was small because many families, as they increased in size, moved to the suburbs where they could not be followed adequately.

Of the thirty-one families surveyed, twenty-one had two children and ten had three. In twenty-six instances both siblings, or the two older siblings in families with three children, were of the same sex. In only five were the sexes different. The reasons for the overwhelming preponderance of siblings of similar sexes (26:5) will be discussed subsequently. Of the twenty-six similar sets, seventeen were males and nine were females. The age difference was uniformly small. Twenty-four were 1 to 3 years apart, one set 3½ and one 4½. (In families with

three children this span refers to that between the two older siblings.) The limitation in the present study to consideration of the twenty-six sets of siblings in whom the sexes were similar was based on the contention that this situation presented normal rivalries and comparisons in their most acute form.

The majority of families were in the middle and upper economic brackets; a few in poorer circumstances. Twenty-two were Jewish. Most families lived in New York City apartment dwellings, a few in the suburbs; divorce occurred in two families; marital difficulties were overt in an additional three; in one family, the mother had a serious mental illness requiring institutional treatment. Most families did not employ nurses or governesses; in no family did the presence of a nurse seem to bear directly on the problem under discussion. In only two families was the mother away from home at business during the entire day.

SIBLING CATEGORIES

The behavior patterns and attitudes of the twenty-six sets of siblings could be characterized as follows:

1. A normal older child and a disturbed second child.
2. Both siblings disturbed with the younger showing greater frequency and intensity of symptoms.
3. Both siblings disturbed with the older showing greater frequency and intensity of symptoms.

Group I.—The first, and by far the largest, grouping of *a normal older child and a disturbed second child* included nineteen sets of siblings, of whom eight were the two older children of the ten families with three children. With minor exceptions, the older siblings were intelligent, happy, cooperative, alert, and active. They exhibited simple childhood fears and problems from time to time but aside from hyperactivity in two children, wakefulness at night in one, and poor eating habits in another, behavior could be considered normal. Furthermore, some who had shown evidence of being overprotected earlier in life had become less tense by the time the second child arrived.

In these nineteen families, however, the second child, somewhere between 1 and 3 years of age, began to show symptoms of unhappiness and frustration. Common indications were a slowing in speech development, poor eating and sleeping habits, severe crying spells, excessive quietness, and resistance to bladder training. Other children were restless, destructive, withdrawn, and willful. One begged constantly for assistance so as to draw attention to herself; another reacted bitterly to unsuccessful attempts at imitation of the older sibling. Still another spoke poorly; his older brother answered all questions intended for him. Another restless child refused to be left alone, had temper tantrums, and appeared to sense the difference in her mother's attitude. She was cared for by a nurse while her mother attended the older daughter. Others masturbated continually, rocked on hands and knees, banged their heads, stamped their feet, or stuttered.

One 15-month-old child engaged in temper tantrums when he failed to master his older brother's jigsaw puzzle. Another infant aged 15 months, while in the country, was placed in a play pen in the garden most of the time and was left to her own devices while her parents drove off with the

older daughter. The infant, formerly contented when in the city, began to manifest symptoms such as excessive thumb-sucking and then hair pulling to the point where she veritably depilated the entire right side of her scalp.

Group II.—The second group, in which both siblings were disturbed, with *the younger showing greater frequency and intensity of symptoms*, consisted of five sets including one from a family with three children. In each instance, the older child prior to the birth of the second sibling was characterized as restless, nervous, difficult to train, fearful, and given to nail biting. Crying and vomiting, jealousy, and enuresis were also present. The younger sibling in three cases, between 1 and 3 years of age, exhibited all of the symptoms of the first born but to a more pronounced degree and added such aberrant behavior as fits of temper, throwing of objects, extreme anger, and destructiveness. In the other two cases, the children who were somewhat older displayed an inability to concentrate, wildness, and a tendency to run away from home. In one of the families, the second child was unusually small and was more subdued than the first. He resented being treated like a baby, spoke late, and stuttered. In this family, the older child answered all questions directed at the younger.

Group III.—Only two families were included in the third grouping in which *both children were disturbed with the older showing greater frequency and intensity of symptoms.* Characteristics listed in the previous groups were also apparent in these cases. Most obvious was the marked inability on the part of each older child to accept the second sibling. Furthermore, in one case, the father's prolonged absence from home during the World War II, and in the other overt marital disharmony, resulted in abnormal situations.

THREE-CHILD FAMILIES

In families with three siblings no patterns could be established relating the middle child's behavior to the arrival and existence of the third. At times, however, the problems of the second child were aggravated following the birth of the third child. It is interesting that no unusual behavior pattern appeared in the third child in nine of the ten families with three children. In only one of them was there brief rebellion. It seems likely that by the time that two children are in the home the parents' attitudes are sufficiently labile that no special conflict arises with the arrival of the third sibling. This was true even in families in which difficulties were encountered with the second born.

MATERNAL PREOCCUPATION WITH THE OLDER SIBLING

The underlying reason for the preferential treatment of the first born appears to lie in the mother's intense preoccupation with the first child. This preoccupation stems from feelings of inadequacy revealed by the mother during her care of the first child. He is her introduction to parenthood. Her sense of responsibility is enhanced and she tends to exaggerate the importance of her child.[6] In the early months also there is a strong fear that the infant will not survive and, following this initial stage, a highly developed desire to protect him. As the child grows older, the mother may be reluctant to impose restrictions and discipline for fear that they will make the youngster

unhappy or thwart him psychologically. This unwillingness to say "no" to a child can eventually become a difficult habit to break. In addition there is the mother, who, in her desire to become a "perfect" parent, devotes too much time and attention to her child. Perfection to her means constant association with and direction of her offspring. When the second child is expected or is already on the scene, attitudes such as these become mere rationalizations of the valid concept that the first child must be adequately prepared for the second. As a consequence, the mother's fear that she might neglect her first born makes her concentrate her attention and affection on him all the more after the second baby arrives.

OTHER REASONS FOR PREFERENTIAL TREATMENT OF FIRST BORN

Other underlying reasons for the mother's behavior may not come to the pediatrician's attention. An unsatisfactory marriage, severe neurotic symptoms in the husband or herself, death of her parents in early life, loss of a previous child, and fear of hereditary illnesses are some of the causes that the pediatrician may be unable to identify readily. On the other hand, in many instances he finds that the problem can be narrowed to very simple terms. For example, when the family lives in cramped quarters and the mother, for economic or psychologic reasons, is always at home, the physical closeness may color the entire parent-child relationship. Often, too, when the second sibling is of the same sex as the first, the parents may be disappointed and unconsciously reject the second child. Grandparents, also, often cherish the older sibling and find the second uninteresting, by comparison, in the crucial early years. Maternal manifestations of rejection may be revealed in such commonplace phrases as "the second is no bother at all," "I'll certainly let this one cry more," "I may have spoiled my first but I'm taking no chances of this with the second." An unwitting confirmation of this attitude is the mother's casual boast to the pediatrician that she no longer has need to refer to the baby manual which she formerly considered a bedside bible in the rearing of her first child. Aggravating the situation may be the perceptive older child, who, sensing his mother's preoccupation with him, communicates his importance and self-confidence to his younger brother, thereby intensifying the second's feeling of an inferior status. Or the older child, afraid of forfeiting his senior and superior claim to his mother's love and attention, may disparage the progress of his younger brother and engage him in competitive activities in which he is sure to emerge victorious if only by reason of his age and size. In the continual rivalry between siblings of the same sex, the younger one's failures to equal or surpass the older become more disastrous when the children do not share equally in the parents' interest and affection.

ROLE OF THE FATHER

The role of the father was difficult for the pediatrician to assess. During most of the visits to the home or office, the father was necessarily absent and his relationship toward the child could not be accurately evaluated. But superficial and occasional observation and questioning indicated that fathers in the twenty-six families under dis-

cussion manifested the general behavior patterns evident in any average family. Some enjoyed their children, spent as much time as possible with them, participated in their care and could be considered "good" fathers. Others were bored, impatient, ineffective, or critical. In this study no outstanding pattern of paternal behavior could be related causally to the problems of the second sibling.

DISCUSSION

A review of the twenty-six families warranted the following deductions: The second child, in all but two instances, exhibited the more pronounced symptoms of abnormal behavior. Where symptoms were also manifested by the first born, they were not as numerous, frequent, well-defined, or intense.

Often the younger sibling appeared placid, relaxed, and happy during the early months in spite of the mother's preferential treatment of the first born. When this occurred, the mother, taking advantage of this seeming self-sufficiency, tended more and more to leave the child alone, thereby arousing a feeling of neglect which was later to manifest itself. Symptoms appeared when the second child was generally between 1 and 3 years of age and learning to walk, talk, and develop various skills. It is then that he begins to "use the first born as his pacemaker with the ever present drive to overcome and surpass him."[6]

It was also determined that the second child's symptoms were more pronounced in cases where the first born was disturbed, than in those instances where the older child was well-adjusted.

Comparisons of male and female sets of siblings revealed a greater tendency toward aggressive behavior and competition on the part of the males. Because the younger male feels competition more strongly, symptoms of unhappiness and frustration are more evident in second male than in second female siblings.

MANAGEMENT

In most cases where the symptomatology was identified by the pediatrician and the causes understood by the parents, simple treatment was effective. Specific suggestions included division of love and attention between the siblings on an equal basis according to their needs; inclusion of the younger child in the family group as often as possible, yet demanding less of him than before; discouraging sibling competition whenever possible; separation of siblings in play and nursery groups; encouraging separate sets of playmates; and, where feasible, helping the older child to understand the younger and cautioning him to permit the younger to talk and play in his own fashion. At the same time parents were reminded that each child might require different handling and that they themselves might be different than when their first child was born. Suggestions such as these worked with remarkable success and by the time the second child was 5 or 6 years old most of the symptoms had disappeared to a large degree. In four cases, psychiatric care seemed indicated and was advised.

It is advisable that the pediatrician adopt a reassuring attitude during discussions of therapy with the mother, so as not to increase her feelings of guilt. These conversations must not

of course take place in the presence of the disturbed child and should be addressed to all adult members of the household. The father, in particular, ought to be included so that he can be instructed in the same course of conduct to be carried out by the mother.

The pediatrician cannot be expected to determine all of the causes for the parents' insecurities. In some situations, even after the mother comes to realize that she may be able to shed some light on the reasons for her overattachment to her first child, she is loathe to discuss the personal aspects of her situation with the pediatrician. Ashamed of her problems and highly secretive, she is sometimes resentful of even the most tactful questioning. Psychiatric consultation in these cases can be suggested and may be accepted by the mother.

However, in most cases the pediatrician's advice is gratefully acted upon. Obviously, though, the best course is to attempt prevention of the situation in the first place. This can only be done by making the mother aware, as early as possible during the infancy of her first born, of the dangers inherent in an overattachment and solicitation of the baby. In this way guilt feelings will not be aroused toward her first child when her love and attention must necessarily be divided in the future. The establishment of such an attitude would appear to be the basic way of avoiding consequent harmful effects on the younger sibling.

The valuable suggestions of Drs. Harry S. Bakwin, Abram Blau, and Richard L. Frank, and the editorial help of Mrs. Carol S. Diamond, are gratefully acknowledged.

REFERENCES

1. (a) Levy, D. M.: Rivalry Between Children in the Same Family, Child Study **2**: 233, May, 1934.
(b) Levy, D. M.: Studies in Sibling Rivalry, Research Monograph, American Orthopsychiatric Association, No. 2, 1937.
2. Wile, I. S., and Jones, A. B.: Ordinal Position and Behavior of Young Children, J. Genet. Psychol. **51**: 61, Sept., 1937.
3. Jones, H. E.: Order of Birth in Relation to the Development of the Child, in Murchison, C.: Handbook of Child Psychology, Worchester, Mass., 1931, Clark University Press, chap. 7, p. 204.
4. Jones, M. C., and Banks, B. S.: Personality Development in Childhood, Monograph, Society for Research in Child Development **1**: No. 4, 1936.
5. Oberndorf, C. P.: Psychoanalysis of Siblings, Am. J. Psychiat. **8**: 1007, 1929.
6. Strauss, B. V.: The Dynamics of Ordinal Position Effects, Quart. J. Child Behavior **3**: 133, April, 1951.

Comments on Current Literature

VIRUS INHIBITION BY AMINO ACIDS

WHATEVER their fundamental nature, viruses and rickettsiae must be considered obligate intracellular parasites since for growth and reproduction, they require the intracellular environment of a living cell. These disease-producing agents appear to be lacking in one or more enzyme systems which must be borrowed from susceptible host cells. Their dependence on micro-molecular components of living cells suggests a possible approach to the control of infection due to viruses and rickettsae, by alteration of the host in some manner which would render the intracellular environment unsuitable to the needs of the infectious agent.

Fundamental studies concerning the effects of certain amino acids on the multiplication of viruses have shown that, under experimental conditions at least, some degree of control of virus infection is feasible. In the July, 1951, issue of the *Proceedings of the Society for Experimental Biology and Medicine,* Eaton and his associates[1] reported the results of investigations with mumps and influenza viruses which indicated that certain amino acids retard the growth of these viruses in tissue culture. In these studies minced chorioallantoic membrane of the embryonated hen's egg was used in tissue culture preparations, and virus multiplication was measured by means of the hemagglutination of chicken erythrocytes. In some instances virus multiplication was measured by titrations of the infectivity of the virus. These results indicated that the amino acids, l-arginine and dl-lysine, do bring about inhibition of viral growth even in low concentrations of from one to two milligrams per milliliter. L-lysine appeared to be approximately twice as effective in inhibition as the dl- form. Particularly in the case of arginine, which was studied in greater detail than were the other amino acids, the effect was shown to be not one of inactivation of the virus itself, but rather that the amino acid exerted some effect on the host cells, or entered into the interaction of the host cell and the virus in such a way as to interfere with virus propagation. This inhibitory effect of arginine was shown by withdrawal of the amino acid to be reversible, and the changes brought about by the amino acid seem to take place in the absence of any demonstrable alteration in oxygen consumption, cellular utilization of glucose or growth potential of the tissue.

Another excellent report dealing with virus growth and virus inhibition, which appeared somewhat earlier, was that of Ackermann[2] in the *Journal of Experimental Medicine,* April, 1951. Here Ackermann discusses the role of the amino acid, l-methionine, in the biosynthesis of the influenza virus, PR8-Type A. Ackermann has been able to show by carefully controlled experiments that l-methionine is required in the host-virus interaction system for the propagation of the influenza virus. Likewise under controlled conditions, dl-methoxinine and dl-ethionine were shown to prevent multiplication of the influenza PR8 virus. It was apparent from these studies that the inhibitors of virus multiplication do not bring about their inhibitory effects by destroying the virus itself, by destruction of the host tissue, nor by preventing virus invasion of the host cell, but by interference with the synthesis of the virus. The inhibitory action of dl-methoxinine and

dl-ethionine was blocked effectively by the addition of l-methionine.

Eventual therapy in human subjects, where the infectious agent is viral in nature, is suggested by observations such as these. The concept is an important one from the clinical point of view: that interference with the multiplication of virus can be accomplished effectively by the addition of inhibitors, which for whatever reason, prevent the utilization of specific substances required for viral synthesis. These therapeutic implications have been emphasized further by animal experiments such as those of Sprunt[3] with mice. Mice which had been kept on a low protein diet showed increased resistance to infection with the swine influenza virus, indicating that a poorly nourished cell is in some manner less favorable for the growth of virus. The effect of protein inanition on the host can be reduced by feeding the animal methionine. Ackermann points out that "one might anticipate that the effective concentration of methionine would also be reduced by the administration of (one of its antagonists) ethionine or methoxinine along with an adequate diet."

Although this entire field of investigation concerned with virus-host-cell relationship, virus multiplication and inhibition, is a very complex one, it seems clear at the onset from extensive investigations of this type that modification of host-cell metabolism by a variety of substances may interfere effectively with the growth of animal viruses in tissue culture. Principles established by such fundamental studies might very well find application eventually in therapeutic control of virus disease in higher animals.

RUSSELL J. BLATTNER.

REFERENCES

1. Eaton, M. D., Magasanik, Boris, Perry, Maud E., and Karibian, Doris: Inhibition of Influenza and Mumps Viruses in Tissue Culture by Basic Amino Acids, Proc. Soc. Exper. Biol. & Med. **77**: 505, 1951.
2. Ackermann, W. W.: The Role of l-methionine in Virus Propagation, J. Exper. Med. **93**: 337, 1951.
3. Sprunt, Douglas H.: Increased Susceptibility of Mice to Swine Influenza as a Result of Methionine Injections, Proc. Soc. Exper. Biol. & Med. **67**: 319, 1948.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination held at Chicago, Ill., Nov. 30, Dec. 1 and 2, 1951.

Dr. John J. Benton, 213 W. Sixth St., Panama City, Fla.

Dr. Frederick Charles Biehusen, Madigan Army Hospital, Tacoma, Wash.

Dr. Joseph Borenstine, 121 W. 63rd St., Kansas City 5, Mo.

Dr. Warren Guy Bosley, 208 Masonic Bldg., Grand Island, Neb.

Dr. Charles Augustus Branthaver, 2615 Eye St., Sacramento, Calif.

Dr. Robert C. Brownlee, Jr., Durham Bldg., Anderson, S. C.

Dr. Gibson Packer Buchanan, 620 Amberson Ave., Pittsburgh 32, Pa.

Dr. Charles Chi Chang, 3121 Bryan St., Dallas, Texas.

Dr. Roger W. Clapp, Mayer Bldg., Butte, Mont.

Dr. Lawrence Joseph Cohen, 1811 Logan Ave., Cheyenne, Wyo.

Dr. Wildo D. Colon, 6815 Southern Ave., Shreveport, La.

Dr. William Ward Currence, Lt. Col. (MC), 522 Elmhurst, San Antonio, Calif.

Dr. William S. Davis, 2045 E. 18th Ave., Denver, Colo.

Dr. Robert William Deisher, 19070 Ballinger Way, Seattle 55, Wash.

Dr. Robert M. Eiben, 3561 Radcliffe Rd., Cleveland Heights 21, Ohio.

Dr. Herman Murray Eisen, 6230 Wilshire Blvd., Los Angeles 48, Calif.

Dr. Luke L. Ellenburg, P. O. Box 186, Greeneville, Tenn.

Dr. Mary Allen English Engle, 6908 Millbrook Blvd., St. Louis 5, Mo.

Dr. Harry William Farrell, 607 Nat'l Bank of South Dakota Bldg., Sioux Falls, S. D.

Dr. William Matthew Featherston, 1705 W. Second St., Elk City, Okla.

Dr. Edward George Forgrave, 14001 Greenfield, Detroit, Mich.

Dr. Gerald I. Freeman, 1120 Grand Ave., St. Paul 5, Minn.

Dr. Joseph A. Garrisi, 3404 West Beverly Blvd., Montebello, Calif.

Dr. Gene H. Grabau, 9710 Lookout Dr., St. Louis, Mo.

Dr. William V. Gross, Jr., 1714 E. Monument St., Baltimore 5, Md.

Dr. David Tirrell Hellyer, 722 South Kay St., Tacoma, Wash.

Dr. Alfred Hicks, II, 1592 Madison St., Denver, Colo.

Dr. Pope B. Holliday, Jr., 837 McCallie Ave., Chattanooga, Tenn.

Dr. Isabel Essig Jones, 2131 University Ave., Berkeley 4, Calif.

Dr. Gordon Arthur Kagen, 224 N. Fifth St., Reading, Pa.

Dr. Chester T. Kasmersky, 997 Studer Ave., Columbus, Ohio.

Dr. William F. Ketchum, 2106 Ferndale Ave., Baton Rouge, La.

Dr. Leonard L. Kishner, 1217 E. 30th Pl., Tulsa 5, Okla.

Dr. Harvey Kravitz, 2514 W. Devon Ave., Chicago 42, Ill.

Dr. Hernandez Gustave LaBranche, U. S. Army Hospital, Fort Leonard Wood, Mo.

Dr. Emanuel C. Liss, 104 S. Main St., South Bend, Ind.

Dr. Richard Seymour Logan, 410 S. Second St., Elkhart, Ind.

Dr. Franklin Lynch, Bay Street, Westport, Conn.

Dr. Robert William McCammon, Child Research Council, 4200 E. 9th Ave., Denver, Colo.

Dr. Charles Q. McClelland, Capt. (MC) 0-1747079, 10th Field Hosp., APO 800, c/o Postmaster, New York, N. Y.

Dr. Logan U. Mewhinney, 6115 La Vista, Dallas, Texas.

Dr. Roxie Tyler Mudgett, Dept. of Path., General Hospital, Louisville 2, Ky.

Dr. Franklin Albert Munsey, 321 W. State St., Rockford, Ill.

Dr. James Moss Patton, 264 Paulsen Medical & Dental Bldg., Spokane, Wash.

Dr. Floyd Russel Peterson, 6228 3/4 West Manchester, Los Angeles 45, Calif.

Dr. John Belvin Reinhart, Bowman Gray School of Medicine, Winston-Salem 7, N. C.

Dr. Lionel H. Rothenberg, 2905 LaBranch, Houston, Texas.

Dr. Albert John Schroeder, 3519 Girard Ave., South, Minneapolis 8, Minn.

Dr. Jerome T. Y. Shen, 4660 Maryland Ave., St. Louis 8, Mo.

Dr. Frederic Speer, 2601 Parallel Ave., Kansas City 2, Kan.

Dr. John Latshaw Steigerwalt, 1330 W. Montgomery Ave., Rosemont, Pa.

Dr. James T. Van Biber, 317 W. Kansas, Independence, Mo.

Dr. Stanley Vangrov, The Doctor's Bldg., 2676 Salem Ave., Dayton, Ohio.

Dr. Bailey Webb, 300 Swift Ave., Durham, N. C.

Dr. James P. Whittemore, Mayer Bldg., Portland 5, Ore.

Dr. George Andrew Zirkle, Jr., 608 W. Main Ave., Knoxville, Tenn.

St. Christopher's Hospital for Children, in cooperation with the United Cerebral Palsy Fund and the Department of Pediatrics of the Temple University School of Medicine, announces the establishment of a Diagnostic Service for Neuropathologic Studies of Cerebral Palsy.

The facilities of any single institution for investigation of neuropathologic problems are limited by the relatively small number of autopsies performed on children with neurological disorders, and by the inaccessibility of facilities for detailed histologic examination of the central nervous system. This new service, under the direction of Dr. James B. Arey and Dr. Waldo E. Nelson, with Dr. Ernest Spiegel as consulting neuropathologist, has been formed in an effort to make these facilities available to more physicians and hospitals.

The purpose of this service will be to correlate the clinical course and pathologic findings in children in whom:

1. A disease of the central nervous system is suspected or
2. The diagnosis of cerebral palsy has been entertained or established.

The institution submitting a clinical history and a brain from such a patient will receive a detailed report, together with a pertinent bibliography and representative histologic sections within six months after the specimen is received. Transportation costs and suitable containers will be furnished upon application to Dr. James B. Arey, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33, Pa.

In October, 1951, a conference was held in Zürich, under the chairmanship of Prof. Fanconi, of the **International Paediatric Association** to discuss "Pediatric Abstracts." Representatives from France, England, Germany, Spain, Italy, Holland, and the United States attended. A number of suggestions were adopted to be sent to the presidents of national pediatric associations and to the editors and publishers of pediatric journals. Among these was that of the three "abstract journals" represented at the conference: *Courrier* should continue publishing indicative abstracts while *Excerpta Medica, Section on Paediatrics* and the *Zentralblatt für Kinderheilkunde* should publish informative abstracts. The discussion brought out the difficulties of abstracting. Authors' abstracts are likely to be subjective rather than objective, while abstracts prepared by others are very uneven in quality and may omit important data. It was suggested that notices of important articles from clinics and research foundations be sent directly to the three abstract journals by the heads of services. The ultimate use of such notification would rest with the Editors.

The publishers of the three journals were requested to allow the free use of ten abstracts a month to the pediatric groups of certain nations for publication in their own language. It was further suggested that pediatric journals in infrequently used languages provide a summary in English, French, German, Russian, and Spanish.

The Louis Lefkoe Memorial Foundation of Philadelphia has offered a prize of $500.00 for the most worth-while original contribution to the medical knowledge of Cerebral Palsy. The paper is to be in the customary format for publication of medical literature. It may cover any aspect of the subject, such as pathogenesis, biochemical knowledge, pathology, diagnosis, treatment, etc. The paper is to be submitted to the Trustees of the Foundation on or before Sept. 1, 1952.

The **University of Louisville School of Medicine** announces the appointment of Dr. U. Pentti Kokko as Associate Professor in Child Health Research.

An interesting educational development is the appointment of a sociologist to the department of pediatrics at **Yale University Medical School.** Support for the research assistant has been provided by the Russel Sage Foundation.

Book Reviews

Studies of Undernutrition, Wuppertal, 1946-49. Members of the Department of Experimental Medicine, Cambridge, and Associated Workers, Medical Research Council Special Report Number 275, London, 1951, His Majesty's Stationery Office, 404 pages. Price 12s.6d.

This book reports the results of more than three years of investigation concerning "the effects of undernutrition on the physical and moral well-being of a modern community." The work was directed by Dr. R. A. McCance, Professor of Experimental Medicine, Cambridge, and Dr. Elsie Widdowson of that department. Under them a team of workers conducted the investigations here described in laboratories of the I. G. Farbenindustrie, and in wards of the Municipal Hospital of the German industrial city of Wuppertal, between June, 1946, and January, 1949. Nutritional conditions in this region did not become stringent until 1946, reached their worst phase in the winter of 1946-47, and were not alleviated until the summer of 1948. Although never reaching a stage of mass starvation, these immediate postwar (and post-bombing) circumstances provided mass undernutrition of a large civilian population. To these unfortunate people living on a daily (adult) ration of 1,000 to 1,500 calories, was added a constant inflow of particularly ill-nourished prisoners of war returning from Russia. Several hundred of these men were studied, many of them throughout the period of rapid weight gain which occurred under extra food rations provided at their repatriation. This large and varied number of undernourished people of all ages under study, the excellent laboratory facilities and training of the investigators, the unhurried nature and the diversity of their studies, all make this volume particularly valuable for students of nutrition. The well-founded status of Professor McCance and Dr. Widdowson in what might be called the scholarship of science makes it essential.

To review here twenty-eight chapters, each of which recounts a complete investigation of one aspect of clinical undernutrition, is an obvious impossibility. To indicate something of the scope of studies, a few chapter headings may be mentioned: Hepatic structure and function, Emotional disturbances and behavioural reaction, Serological responses to antigenic stimuli, Serum cholesterinases, Cardiac output and circulation, Capillary resistance and permeability, Absorption and excretion of nitrogen, calcium, magnesium and phosphorus—researches upon these are scattered among numerous other subjects whose inclusion would be more predictable. A 45-page chapter on the history, significance, and etiology of hunger edema, contributed by Professor McCance, utilizing a bibliography of some 500 sources, is perhaps outstanding. Among its conclusions, the implication of the role of posture as significant in relation to this unsolved problem is substantiated by investigations of body fluids and renal function in two other chapters.

Of especial interest to pediatricians are the researches by R. F. A. Dean on the size of the infant at birth and the yield of breast milk, and by Mavis Gunther and Jean Stanier on the composition of human milk. Dean took especial pains to avoid the introduction of errors associated with such factors as maternal age and parity, and duration of pregnancy. Allowing for all such factors, he found that the period of most severe undernutrition was marked by an average reduction of birth weight of 185 grams, a very small reduction in birth length, and a decrease in the amount of breast milk obtained by the newborn infant. The moderately reduced amount of breast milk was shown by Drs. Gunther and Stanier to be nevertheless of generally similar composition to that secreted by better nourished control mothers.

A lingering impression of resiliency and adjustability as features of the human organism under nutritional stress persists in the reader's mind after perusal of this book. Numerous alterations, especially in body weight, in amount and distribution of body fluids, and in the emotional aspects of personality are clearly shown to accompany pro-

longed undernutrition. But in many other and perhaps as fundamental aspects, little if any alteration was shown. And the strong tendency to restitution of all measurable changes with the return of calories is, on the whole, further testimony to the body's success in meeting unfavorable nutritional circumstances.

C. A. S.

Summer's Children. Barbara Morgan, Scarsdale, N. Y., Morgan & Morgan. Price $5.00.

This is an unusual and remarkably fine collection of over 200 photographs of children taken at summer camps, showing the varied activities of camp life. It is estimated that several million children go to camps of one kind or another every summer, and the activities and health conditions of camps have long been of interest to pediatricians. This is not a manual of camp organization, group activities, etc., but a graphic picture of what the child does at a camp and how he lives. The photographs are justly entitled to the term superb, and are beautifully reproduced. We know of no other book or collection that has so well presented the emotional reactions of normal healthy children.

It is a book that every pediatrician will enjoy looking through, and it is a splendid book for the waiting room of the office as it will interest not only the children but their parents. It is an artistic book that has a tremendous human appeal. Some may recall seeing a few of the pictures appearing in *Life* a number of weeks ago.

Health Observation of School Children. George M. Wheatley, M.D., and Grace T. Hallock, New York, 1951, McGraw-Hill Book Co., 491 pages. Price $4.75.

This is a text intended to help teachers understand the growth and development of children, and the various diseases and factors that affect the health of the school child. The material is well chosen and clearly presented in as nontechnical a way as is possible in presenting scientific facts and knowledge. Both authors are well qualified by past work and experience for preparing a text of this type. It should be of great help to teachers in understanding the problems and personalities of the children they see daily in the classroom, and thus in turn of aid in their pedagogical work. The format is excellent.

Diagnostische und therapeutische Technik beim Kinde. Dr. Med. Kurt Nitsch, Stuttgart, 1951, Georg Thieme Verlag (Grune & Stratton, New York Agent), 168 pages. Price DM 14.70.

This is a manual of diagnostic and therapeutic methods used in pediatrics by the head of the Bad Orb Children's Hospital. The text describes the various techniques and methods by systems, and practically all of the ordinary and unusual procedures are described. So much is included that many procedures are very sketchily described. Its use would be for a reference text for those who read German.

American Pediatric Directory, 1951-1952. Fifth edition. Joe T. Smith, M.D., Knoxville, Tenn., Editor and Publisher, 226 pages. Price $7.00.

This is by far the most complete list of physicians majoring in pediatrics, as it contains the records not only of those who have been "certified" or restrict their practice to pediatrics, but includes a large number of practitioners whose chief interest is in the field. In addition, the resident staffs of the children's hospitals are included. According to the Editor, almost 9,000 names are included. Names and biographies are listed by states and cities, and an alphabetical list of the names is included.

Healthy Babies. Fifth edition. Josephine Hemenway Kenyon, M.D., and Ruth Kenyon Russell, M.D., Boston, 1951, Little, Brown & Company, 317 pages. Price $3.00.

This is a revised fifth edition of a well-known text for mothers on the care of the baby.

Chronology of Ophthalmic Development. Arthur H. Keeney, M.D., Springfield, Ill., 1951. Charles C Thomas, 22 pages with 3 charts. Price $2.00.

The author has presented in three large charts the prenatal and postnatal development of the eye and the development of vision. The charts are subdivided showing the stage of development of the various parts of the eye as the retina and cornea at different age period levels.

Editor's Column

SIR ROBERT HUTCHISON, BT., M.D., F.R.C.P.

THE October issue of the *Archives of Disease in Childhood* is dedicated to Sir Robert Hutchison on the occasion of his 80th birthday. In addition to a number of scientific contributions by former associates, there are two delightfully written sketches of "Bobby Hutch" as he was known by many generations of house officers and medical students. Both Kenneth Tallerman, who reminisces on his association at the Great Ormand Street Hospital, and A. G. Maitland-Jones at the London Hospital, have succeeded in a few hundred words in picturing the unique flavor and character of the man. A third article by Langley Porter, "Robert Hutchison at The London Hospital Circa 1900: Reminiscences of a Clinical Clerk," gives a picture of Hutchison in his early years and of other clinical teachers in London at the beginning of the century.

Hutchison is best known to American physicians through his book *Lectures on Diseases of Children*, first published in 1904, which went through seven editions to 1936. Two subsequent editions were edited by Alan Monerieff. Hutchison was a prolific writer. Not only is his name associated with thirteen other books, but a bibliography lists 276 published articles from 1895 to 1950.

Hutchison has been greatly honored by his colleagues—he was president of the Royal College of Physicians in 1939, 1940, 1941—and was greatly admired and held in affection by his associates, house officers, and the countless students who studied under him. He belonged to the group of splendid clinical teachers whose counterpart is rarely found in these days of the scientific era of medicine.

One of the best tests of a teacher's ability and influence is how his sayings and teaching are remembered. Dr. Donald Hunter has collected for the issue some of the wisdom and the dry and caustic humor of Hutchison from his writings, and from the reminiscence of a number of his house officers.

In a lecture on diagnosis he wrote:

> Judgement seems to be an inborn faculty, the result of a union of mind and character, which a man either has or has not, and it is almost as difficult for him to increase it as to add a cubit to his stature.
>
> It is quite impossible that you should always be right in your diagnosis, if only for the reason that disease does not always play the game. It is better, however, to be wrong on sound principles than right by chance. Guessing is to be avoided at all costs; for if you once get into the habit of guessing you are diagnostically damned.

At Ormond Street he is quoted by one of his former clerks as referring to his clerks as "A curious collection of crapulous cretins creeping from crib to crib."

Another story from the outpatient department of Ormond Street where Bobby Hutch was presiding:

> A fat Cockney woman brought in a dirty, thin, active baby, who succeeded in drowning the conversation, and threw all the toys to the floor. He then made an attempt on Robert's gold watch. Noticing that the baby

had a mark down one cheek from a discharging ear, Robert seized upon the opportunity to reach for a transfer card, and wrote on it:

"Otorrhoea: to aural department."

"Mother, your baby has a discharging ear. Take it to the ear specialist."

"Oh, doctor, he's attending there these last five weeks."

Giving up the unequal struggle Robert turned to his class:

"Gentlemen, I have recently contracted matrimony. If Providence sees fit to bestow on me progeny and that progeny be the male sex, I shall one day have to consider his future. If he be a brilliant lad far above normal, I shall make of him a physician. If he be merely normal, I shall make of him a surgeon. If he be slightly subnormal I shall make of him a gynaecologist, but, gentlemen, if he be absolutely mentally defective, I shall make of him an ear, nose and throat surgeon.

Sir Robert Hutchison has been a distinguished pediatric leader and teacher who has had a decided influence on the practice of pediatrics. The JOURNAL extends its felicitations on the occasion of his 80th birthday.

MENTAL HEALTH CLINICS FOR CHILDREN

IT WAS only some twenty-five to thirty years ago that the first child guidance clinics were set up on a "demonstration" basis. At that time but few pediatricians were impressed with the need for the better study and treatment of the emotionally maladjusted child. While progress has been made since that time, it has been slow and involved. One of the chief reasons has been the lack of trained and satisfactory personnel to staff the clinics, and a second, the high case cost of such services as compared with the case cost for physical illness. Another reason for the slow progress has been varying concepts as to just where the clinic for mental services is best fitted into the general picture of health services for children. The first idea was that they should be independent isolated institutions or organizations serving the community as a whole. Others felt they should be a part of the school system, or the juvenile court, and some clinics were started on this basis. As medical educators became more alert to the close relationship between mental and physical health, the realization gradually developed that the clinics were probably better connected with existing medical institutions, and in particular with those engaged in teaching. This led to services being developed in some instances by the pediatric department, and in others by the psychiatric department, of the medical schools. In other schools their development took place more logically as an interdepartmental responsibility of the two. Much impetus in the development of mental hygiene clinics has taken place in the last three or four years as a result of funds being made available to governmental agencies for mental health services. However, if the work of the official agency services is to be sound and worth while, the responsibility still lies with the teaching and integrated organizations for training personnel to staff the official agencies at the state or local level.

In a recent report, Pennell, Cameron, and Kramer* have presented data in regard to mental health services for children collected in preparation for the Mid-Century White House Conference. They found that in 1950 there were 1,228 mental hygiene clinics operating in the United States of which 902 served children. There were only 850 clinics operating in

*Mental Health Clinic Services for Children in the United States, 1950, Pub. Health Rep. 66: 1559, Nov. 30, 1951.

1947, and 100 of these had been discontinued by 1950. About one-third of the reporting clinics served children only, and these varied considerably as to the age limitations of the patients treated. There is a decided geographic unevenness in the distribution of the clinics. Fifty-three per cent are in the Northeast section of the country with 1.67 clinics per 100,000 of population, contrasted with 15 per cent in the South with 0.39 clinic per 100,000 of population, or roughly a 4:1 ratio.

The 902 clinics which reported as serving children treated 143,002 child patients during a twelve-month period 1949-1950, or 3.3 patients per 1,000 of child population. There are decided variations in the operation of the clinics. Only 41 per cent of 762 clinics serving children could be considered as operating on a full-time basis. About two-thirds had what is considered a basic staff of psychiatrist, psychologist, and social worker. Some 87 per cent of the full-time clinics are basically staffed. Very few clinics reported a pediatrician or a nurse on the staff. About 90 per cent of the clinics offer diagnostic and treatment services, and in the remainder the service is limited to diagnosis.

It is apparent that after twenty-five years of experience and trial no clear-cut pattern has evolved of the organization and operation of mental health services for children. The report does not go into such important factors as the quality of service rendered, or the results of clinic service. Another unanswered question is the extent of the need for mental health services for children and how they are being met by existing agencies. That approximately 10 patients per 1,000 children under 18 years of age attended the clinics in some states like New York and Montana, and less than 1 per 1,000 children in states like Indiana and Texas, can hardly be attributed to geographic differences in the frequency of mental health problems of children. It is rather that there is a marked difference in how the needs are being met in various parts of the country.